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LATE PRENATAL SYPHILIS

WITH SPECIAL REFERENCE TO INTERSTITIAL KERATITIS: ITS PREVENTION AND TREATMENT

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No phase of the problem of syphilis should be of greater interest to the physician than prenatal syphilis. The symptomatology is diverse; the sequelae if the condition is undiagnosed and untreated are devastating, and the toll to the community is great.

Read at the Fifty-Ninth Annual Meeting of the American Dermatological Association, Inc., Swampscott, Mass., June 4, 1936.

Names with an asterisk represent members of the United States Public Health Service. Names without an asterisk represent members of the Cooperative Clinical Group.

This paper is a part of a symposium on syphilis presented at the annual meeting of the American Dermatological Association. The discussion on the symposium follows the article by Drs. Dennie and Miller, this issue, p. 591.

The survey was conducted by the cooperation of the clinics for syphilis of the Western Reserve University, the Johns Hopkins University, the Mayo Clinic, the University of Pennsylvania and the University of Michigan, assisted by the United States Public Health Service and supported by a special fund contributed by an anonymous donor.

The time to attack prenatal syphilis is while the child is still in utero. The Cooperative Clinical Group [1] has already shown in a previous communication how successful prenatal treatment may be. In some cases, however, the true condition is discovered only after birth. If that is the case, treatment of syphilitic infants in the first two years of life is much more advantageous than treatment given after that period. This phase of the subject has been so fully covered in numerous publications that the present communication is limited to a report of a study of late prenatal syphilis as observed in the five cooperating clinics, special stress being placed on the most frequent manifestation of the disease—interstitial keratitis. It is hoped to recommend means of preventing the appearance of this grave lesion or, if it is already present, of healing it with as little residual damage to vision as possible.

TABLE 1.—*Cases of Late Prenatal Syphilis Classified as to Sex and Color of Patients and Stage of Infection on Admission*

Stage of Late Prenatal Syphilis on Admission	Male		Female		White		Negro		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Acute lesions	108	24.1	117	20.8	182	25.8	43	14.1	225	22.3
Chronic lesions	115	25.7	163	29.0	223	31.6	55	18.0	278	27.5
Inactive stage with residual scars	43	9.6	67	11.9	86	12.2	24	7.9	110	10.9
Latent syphilis	182	40.6	215	38.3	214	30.4	183	60.0	397	39.3
Total	448	100.0	562	100.0	705	100.0	305	100.0	1,010	100.0

MATERIAL STUDIED

The patients with late prenatal syphilis in this series were at least 2 years of age on admission. The evaluation of end-results of treatment in the 1,010 cases is based on two years or more of observation and treatment. There were 705 white patients and 305 Negroes in the series. Half of the patients sought treatment because of some active manifestation of syphilis.

For purposes of this study the material has been divided as follows: patients with active acute or chronic lesions, patients with an inactive stage of the disease with residual scars and patients with latent syphilis in whom the only evidence of the disease on admission was a positive serologic reaction of the blood, with or without the other common objective manifestations of congenital syphilis.

Acute lesions are defined as manifestations of late prenatal syphilis which have existed for less than six months, except that for interstitial keratitis the time limit for acute lesions has been arbitrarily set at two months or less. Chronic lesions are classified as active manifestations of duration longer than two months. Inactive stage with scars refers to

1. Cole, H. N., and others: Ven. Dis. Inform. **15**:83-107 (March) 1934.

inactive residues of earlier manifestations, e. g., quiescent scars of the cornea, saddle nose following an old gumma or old hemiplegia with a negative reaction of the spinal fluid.

The proportion of cases of latent syphilis among the Negro patients was twice as high as among the white, the percentages being 60 and 30, respectively. There was, however, no difference as to sex in the active manifestations of prenatal syphilis. It appears, then, that prenatal syphilis runs a stormier course in white than in Negro patients. There is no obvious explanation for this fact.

It is important to note that less than 2 per cent of the patients had received any antisyphilitic treatment in infancy, and only 19 per cent could furnish any history of infantile lesions, such as rhagades or

TABLE 2.—*Principal Diagnosis and Frequency of Each Manifestation on Admission of Patients with Late Prenatal Syphilis*

Principal Diagnosis on Admission	White		Negro		Total Cases		Frequency of Each Manifestation	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Latent syphilis	214	30.4	183	60.0	397	39.3	397	39.3
Involvement of the skin and mucous membrane	28	4.0	9	3.0	37	3.7	57	5.6
Involvement of the bones and joints	50	7.1	18	5.9	68	6.7	115	11.4
Interstitial keratitis	258	36.6	71	23.3	329	32.6	403	39.9
Involvement of the eye (other than interstitial keratitis or atrophy of the optic nerve)	13	1.8	2	0.7	15	1.5	39	3.9
Atrophy of the optic nerve	10	1.4	1	0.3	11	1.1	25	2.5
Nerve deafness	26	3.7	6	1.9	32	3.2	59	5.8
Visceral involvement	12	1.7	5	1.6	17	1.7	37	3.7
Involvement of the central nervous system								
Asymptomatic	24	3.4	4	1.3	28	2.8	57	5.6
Symptomatic								
Meningovascular disease	13	1.8	3	1.0	16	1.5	19	1.9
Dementia paralytica	41	5.8	3	1.0	44	4.4	46	4.6
Tabes dorsalis	16	2.3	..	...	16	1.5	18	1.8
Total	705	100.0	305	100.0	1,010	100.0	1,272	125.9

lesions of the skin and mucosa. Evidently a high proportion of patients with prenatal syphilis survive the first few months of life and remain asymptomatic only to exhibit some active manifestation of syphilis years later.

PRINCIPAL DIAGNOSIS ON ADMISSION

Among the 1,010 patients with late prenatal syphilis, a number were admitted with several manifestations. Table 2 shows the frequency of the principal diagnoses. Interstitial keratitis was the principal manifestation and occurred in approximately one third of the patients (33 per cent); the next largest group (10 per cent) had an involvement of the central nervous system, and in 7 per cent the bones and joints were involved. Other active manifestations occurred in a decreasing percentage of the patients. Thirty-nine per cent had as the only evidence of syphilis on admission a positive serologic reaction of the blood with or without dental stigmas, saber shins or frontal bosses.

GENERAL CLINICAL RESULTS

Of the total 1,010 patients with late prenatal syphilis, 225 were admitted with an early active lesion, and 57 per cent of these had a satisfactory clinical outcome;[2] 32.9 per cent received the maximum benefit from treatment, but crippling stigmas remained; 9.3 per cent showed progress or relapse on termination of observation or treatment. The good results decreased proportionately as treatment was delayed until after the manifestation either had become chronic or had spontaneously healed leaving residual scars. The percentage of satisfactory clinical results dropped from 57 to 30 when treatment was begun after the lesion had become chronic and to 24 when it was delayed until after spontaneous healing had occurred without treatment. There was a definite increase from 9 to 19 per cent in the number of patients who experienced progression or relapse of the infection according to the stage of the lesion when treatment was sought. The advantage of treatment as a preventive of progression in patients with late prenatal syphilis is evidenced by the small percentage (3.5 per cent) of progress of the disease among those in whom treatment was instituted before any active lesion occurred. In fact, of 397 patients who had latent prenatal syphilis on admission 96.5 per cent showed no progression when treated, although the serologic reaction of the blood remained positive in 53.9 per cent.

SEROLOGIC REACTION OF THE BLOOD

The amount of treatment did not appear to affect the reversal of the serologic reaction of the blood. More than half the patients had a fixed positive serologic reaction[3] despite the treatment given. A further 8 per cent had a serologic relapse on termination of treatment. Of the 281 patients in whom the reaction was reversed, 234 exhibited the reversal after the first year of treatment.

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2. "Satisfactory results" refers to cases in which lesions originally present disappeared; if stigmas remained they were not a handicap and there was no evidence of subsequent progression or relapse. The term also refers to cases in which latent syphilis was present on admission and remained latent or in which if an active manifestation occurred there was complete clinical recovery during subsequent treatment and observation. "Unsatisfactory results" refers to cases in which the maximum benefit from treatment had been obtained but crippling stigmas remained, or to those in which patients were admitted with a condition which remained stationary. "Progress or relapse" refers to cases in which the final clinical result was progression or relapse. "Death" indicates that the fatal outcome was due to syphilis or its treatment. When death was the result of other diseases or conditions the case is included under one of the other categories mentioned.

3. Cases in which the serologic reaction of the blood is persistently positive over a period of two years or more are considered as instances of serologic fastness.

INFLUENCE OF THE SEROLOGIC REACTION OF THE BLOOD ON THE CLINICAL OUTCOME

Late prenatal syphilis is generally considered to be associated with serologic fastness. There is much difference of opinion as to the effect of this phenomenon on the course of the disease. Some observers feel that the syphilitic infection is more resistant; others take the view that the persistently positive reaction has no significance or even that with reasonable treatment it may indicate definitely increased powers of resistance on the part of the host. A study of the material in table 4 shows that among patients with acute lesions of prenatal syphilis and a fixed positive serologic reaction of the blood satisfactory clinical results were achieved in 51 per cent, and 12 per cent showed progression or relapse; on the other hand, of those in whom the serologic reaction

TABLE 3.—*Results of Treatment in Terms of Clinical Outcome in Patients with Late Prental Syphilis*

Stage of Late Prenatal Syphilis When Treatment Was Begun	Clinical Outcome									
	Satisfactory		Not Satisfactory		Progress or Relapse		Death		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Acute lesions	129	57.3	74	32.9	21	9.3	1	0.5	225	100
Chronic lesions	84	30.2	130	46.8	52	18.7	12	4.3	278	100
Inactive stage with residual scars	26	23.7	70	63.6	14	12.7	..	...	110	100
Latent syphilis	377	95.0	6	1.5	14	3.5	..	...	397	100
Total	616	61.0	280	27.7	101	10.0	13	1.3	1,010	100

of the blood was not fast, 64 per cent had a satisfactory outcome and only 7 per cent showed progression or relapse. In those patients who had been untreated during the existence of their active manifestations and who subsequently sought treatment at a time when they showed residual scars only, twice as many satisfactory results were obtained when the serologic reaction of the blood was not fast as when it was fast (31 and 15 per cent, respectively). Among these patients the proportion of progression and relapse was greater when the serologic reaction of the blood was fast than when reversal occurred (15 and 10 per cent, respectively). A fixed positive serologic reaction of the blood in a patient with late prenatal syphilis while he has acute lesions or an inactive stage of the disease with residual scars does not justify so good a prognosis as a more labile reaction. In the patient with latent syphilis it does not appear that serologic fastness influences clinical progression or relapse.

TABLE 4.—*Effect of Fixed Serologic Reaction of the Blood on Clinical Outcome in Patients with Late Prenatal Syphilis in Each Stage of the Infection*

Stage of Late Prenatal Syphilis When Treatment Was Begun	Clinical Outcome: Satisfactory Number	Satisfactory Percentage	Not Satisfactory Number	Not Satisfactory Percentage	Progress or Relapse Number	Progress or Relapse Percentage	Death Number	Death Percentage	Total Number	Total Percentage
Acute lesions										
Serologic reaction of the blood										
Fixed	60	51.3	42	35.9	14	11.9	1	0.9	117	100
Not fixed	69	63.9	32	29.6	7	6.5	..	...	108	100
Chronic lesions										
Serologic reaction of the blood										
Fixed	45	27.8	75	46.3	31	19.1	11	6.8	162	100
Not fixed	39	33.6	55	47.4	21	18.1	1	0.9	116	100
Inactive stage or residual scars only										
Serologic reaction of the blood										
Fixed	8	15.4	36	69.2	8	15.4	..	...	52	100
Not fixed	18	31.0	34	58.6	6	10.4	..	...	58	100
Latent syphilis										
Serologic reaction of the blood										
Fixed	203	94.8	1	0.5	10	4.7	..	...	214	100
Not fixed	174	95.1	5	2.7	4	2.2	..	...	183	100
Total										
Serologic reaction of the blood										
Fixed	316	57.9	154	28.3	63	11.6	12	2.2	545	100
Not fixed	300	64.5	126	27.1	38	8.2	1	0.2	465	100
Grand total	616	61.0	280	27.7	101	10.0	13	1.3	1,010	100

TABLE 5.—*Effect of Prolonged Treatment and Fixed Serologic Reaction of the Blood on the Clinical Outcome in Patients with Late Prenatal Syphilis; Stage of the Infection When Treatment Was Begun*

Stage of Late Prenatal Syphilis When Treatment Was Begun	Clinical Outcome: Satisfactory Number	Satisfactory Percentage	Not Satisfactory Number	Not Satisfactory Percentage	Progress or Relapse Number	Progress or Relapse Percentage	Death Number	Death Percentage	Total Number	Total Percentage
Less Than One Year										
Latent syphilis										
Serologic reaction of the blood										
Fixed	22	95.7	1	4.3	..	...	..	...	23	100
Not fixed	9	100.0	..	...	..	...	..	...	9	100
Total	31	96.9	1	3.1	..	...	..	...	32	100
Active or inactive stage										
Serologic reaction of the blood										
Fixed	2	7.4	13	48.2	9	33.3	3	11.1	27	100
Not fixed	5	26.3	11	57.9	3	15.8	..	....	19	100
Total	7	15.2	24	52.2	12	26.1	3	6.5	46	100
Total (less than one year)	38	48.7	25	32.1	12	15.4	3	3.8	78	100
One Year or More										
Latent syphilis										
Serologic reaction of the blood										
Fixed	181	94.8	..	...	10	5.2	..	...	191	100
Not fixed	165	94.8	5	2.9	4	2.3	..	...	174	100
Total	346	94.8	5	1.4	14	3.8	..	...	365	100
Active or inactive stage										
Serologic reaction of the blood										
Fixed	111	36.5	140	46.0	44	14.5	9	3.0	304	100
Not fixed	121	46.0	110	41.8	31	11.8	1	0.4	263	100
Total	232	40.9	250	44.1	75	13.2	10	1.8	567	100
Total (more than one year)	578	62.0	255	27.4	89	9.5	10	1.1	932	100

Patients under 15 years of age with a fixed positive serologic reaction show a higher percentage of satisfactory clinical response than those who are over 15 on admission. This indicates that the earlier syphilis is treated, the better the clinical response. The duration of treatment also plays an important part in this problem. In table 5 results are shown in terms of treatment for less than a year and for more than a year. Of patients with lesions who had a fixed positive serologic reaction of the blood and who were treated for less than a year, 7.4 per cent had a satisfactory clinical outcome, as compared with a similar group of patients treated for more than a year, in whom a satisfactory result was obtained in 36.5 per cent. In similarly treated

TABLE 6.—*Clinical Results in Late Prenatal Syphilis; the Duration of the Period of Observation After the Termination of Treatment*

Duration of Period of Observation	Clinical Outcome							
	Satisfactory		Not Satisfactory		Progress or Relapse		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Patients with Latent Syphilis								
Less than 2 years	269	94.4	4	1.4	12	4.2	285	72.3
2-5 years	71	97.2	1	1.4	1	1.4	73	18.5
6-10 years	25	96.2	..	...	1	3.8	26	6.6
11 years and over	10	100.0	..	...	..	...	10	2.6
Total	375	95.2	5	1.3	14	3.5	394*	100.0
Patients with Active Lesions or Scars								
Less than 2 years	146	37.3	191	48.7	55	14.0	392	65.0
2-5 years	58	40.8	62	43.7	22	15.5	142	23.5
6-10 years	25	42.4	25	42.4	9	15.2	59	9.8
11 years and over	4	40.0	5	50.0	1	10.0	10	1.7
Total	233	38.7	283	46.9	87	14.4	603*	100.0

* The total does not include 13 patients in whom syphilis was given as the cause of death.

patients in whom the serologic reaction of the blood was not fast the percentage of satisfactory outcome increased to 26 and 46 per cent, respectively. These data indicate that the best clinical results are obtained if treatment is instituted as early as possible and is continued for more than a year in patients with clinical manifestations regardless of serologic outcome. These differences were not noted in patients in whom the disease was in a latent stage on admission.

DURATION OF OBSERVATION

Thirty-two per cent of the total number of patients with late prenatal syphilis were under observation for more than two years after cessation of treatment. Among the 603 patients who had had some active manifestation when treatment was begun, 87 (14 per cent) showed progression of the disease despite treatment, whereas of the

394 who began treatment while their infection was in the latent stage, only 14 (3.5 per cent) had progression of the disease on termination of treatment or observation. From table 6 it appears that the mere passage of time did not protect against the possibility of progression of the disease. Proportionately as many patients followed for from two to five and from six to ten years showed progression of syphilis in these intervals as within the first two years of observation.

DISTRIBUTION BY AGE OF PATIENT ON ADMISSION

Patients with late prenatal syphilis come under observation and receive treatment at the clinic during the early years of life. In this series 78 per cent were admitted at from 2 to 15 years of age, as shown in table 7. This situation is undoubtedly due in some measure to the

TABLE 7.—*Proportion of Patients with Late Prenatal Syphilis in Each Age Group in Whom the Disease was Latent on Admission*

	Diagnosis Based on					
	Positive Serologic Reaction of the Blood Only		Active Lesions or Scars		Total	
Age on Admission	Number	Percentage	Number	Percentage	Number	Percentage
2- 5 years	108	62.1	66	37.9	174	100.0
6-10 years	151	43.1	199	56.9	350	100.0
11-15 years	92	34.6	174	65.4	266	100.0
16-20 years	32	27.4	85	72.6	117	100.0
21-25 years	9	14.3	54	85.7	63	100.0
26-30 years	4	22.2	14	77.8	18	100.0
30 and over	1	0.5	21	95.5	22	100.0
Total	397	39.3	613	60.7	1,010	100.0

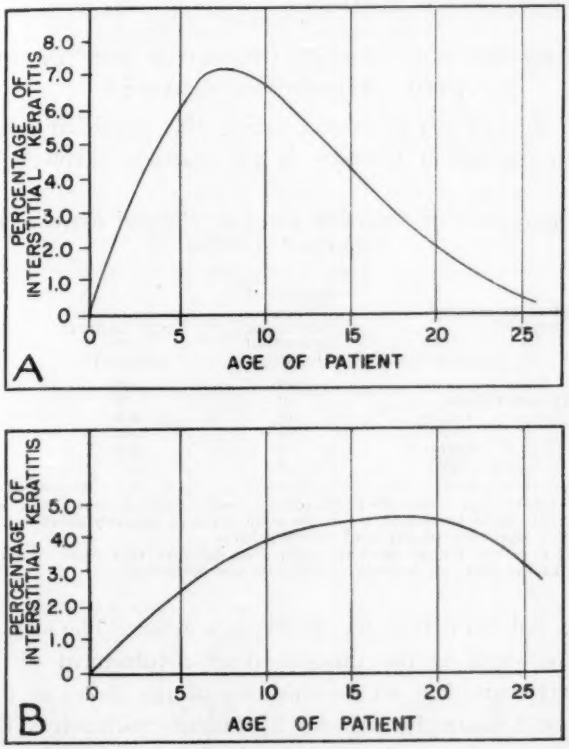
perseverance of the social service department in the various clinics in bringing family groups to the clinic. It appears that as patients become older, more of those who seek treatment do so because of an active condition.

This statement is stressed because of the erroneous opinion frequently held that active lesions of prenatal syphilis, especially interstitial keratitis, usually occur in the 6 to 15 years age period and that once the patient has passed the age of puberty without having had interstitial keratitis his chances of avoiding it are good. It is true that the years of greatest risk are between 6 and 15 years of age, but without the protection of adequate modern antisyphilitic therapy there is no period without risk. The present conception of the period of greatest risk has become established because of the preponderance of patients treated in the 6 to 15 year age period. Curve *A* in the chart shows the percentage of total cases of interstitial keratitis that occur at each age. If the rate of involvement for each year of life at which the patient may exhibit the condition is considered, as shown in curve *B*, it will

be found that patients as young as 3 years of age exhibit interstitial keratitis and that the rate is consistently high up to 20 years of age. Thus an untreated patient with late prenatal syphilis is constantly in danger of showing interstitial keratitis up to the age of from 20 to 25 years.

PROPHYLAXIS OF INTERSTITIAL KERATITIS

Ninety per cent of the patients with interstitial keratitis had been untreated for syphilis before the first attack. Of 884 patients with



A, percentage incidence of interstitial keratitis by age of patient at onset among patients with late prenatal syphilis; *B*, incidence of interstitial keratitis for each year of life, each patient with late prenatal syphilis being considered at risk for every year of observation-treatment life.

untreated syphilis, 314 (or 36 per cent) sought treatment because of interstitial keratitis. In striking contrast is the preventive effect of adequate modern therapy (more than fifteen injections of arsphenamine and an appropriate amount of treatment with a heavy metal). Among 243 patients adequately treated for prenatal syphilis before the onset of interstitial keratitis, only 5 (or 2.1 per cent) subsequently showed

it even though the treatment had not been administered until after the patient was 2 or more years of age. In fact, only 17 per cent of the total 1,010 patients were admitted at or before 5 years of age.

Even inadequate treatment greatly reduced the incidence of interstitial keratitis, the percentage dropping from 36 when no treatment was given to 9 when an inadequate amount was administered. However, three to four times as many cases of interstitial keratitis developed in the inadequately as in the adequately treated patients. Therapy with a heavy metal alone without the accompanying arsenical was found to be absolutely insufficient protection.

PREVENTION OF INVOLVEMENT OF SECOND EYE IN PATIENTS WITH INTERSTITIAL KERATITIS

One of the serious problems facing the physician who treats a patient with interstitial keratitis is the possible involvement of the

TABLE 8.—*Effectiveness of Treatment for Late Prenatal Syphilis in Preventing Interstitial Keratitis*

Amount of Treatment Received*		Number of Patients Exhibiting Interstitial Keratitis	Total Number of Patients†	Percentage Exhibiting Interstitial Keratitis
Arsenical	Heavy Metal			
None		314	884	35.5
Heavy metal alone		10	18	55.6
Little	Little	13	150	8.7
Little	Much	4	43	9.3
Much	Little	4	130	3.1
Much	Much	5	243	2.1

* Little arsenical means from 1 to 15 injections; much arsenical means 16 or more injections. Little heavy metal means from 1 to 30 injections or weeks of mercury rubs; much heavy metal means 30 or more injections or weeks of mercury rubs.

† This total does not include patients treated in the first two years of life or those for whom the age at the onset of interstitial keratitis was unknown.

second eye. All too often this contingency arises. The success of antisyphilitic treatment in the prevention of involvement of the second eye is largely dependent on the duration of the lesion of the first eye when treatment is sought. Among 64 patients with interstitial keratitis affecting one eye who sought treatment in the several clinics, the involvement remained unilateral in 41 (64 per cent). The effectiveness of treatment begun within six months of the onset of the interstitial keratitis in the prevention of involvement of the second eye is apparent from a study of 55 cases, in 71 per cent of which the involvement remained unilateral. From the limited number of cases (55) studied in which treatment was begun early it appears that the involvement of the second eye occurred within the first two years after the onset in the first eye. In fact, it was found that in 50 per cent of the cases in which the second eye became involved it did so within six months, and in 87.5 per cent the extension took place within two years. Therefore, if the

physician treating the first attack of interstitial keratitis has administered adequate antisyphilitic treatment he may feel reasonably certain after two years has elapsed that extension to the second eye will not occur. This statement is based on the fact that 37 of the patients who began treatment within the first six months of onset of interstitial kera-

TABLE 9.—*Prevention of Involvement of the Second Eye in Patients with Interstitial Keratitis by Routine Antisyphilitic Therapy Begun within Six Months of the Onset in the First Eye*

Duration from Onset in First Eye to Onset in Second Eye or to End of Case	Involvement Remained Unilateral	Involvement Became Bilateral	Total
Less than 6 months	1	8	9
6 months-1 year	..	2	2
1-2 years	3	4	7
2-5 years	22	2	24
5-10 years	10	..	10
10 years and more	3	..	3
Total	39	16	55*

* This total includes only patients seeking treatment within the first six months of the onset of interstitial keratitis whose interstitial keratitis was still unilateral when treatment was begun.

TABLE 10.—*Clinical Results from Modern Antisyphilitic Treatment Begun in the Various Stages of Interstitial Keratitis*

	Stage of Interstitial Keratitis at Which Treatment Was Begun									
	Early Acute*		Late Acute		Relapsing		Inactive		Total	
Clinical Results of Treatment	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Satisfactory:										
Excellent	55	35.0	25	28.7	6	10.9	10	7.8	100	23.4
Good	22	14.0	4	4.6	11	20.0	15	11.6	54	12.6
Arrest	...	....	...	....	...	....	34	26.4	34	7.9
Improvement	52	33.1	38	43.7	23	41.8	27	20.9	125	29.2
Total	129	82.2	67	77.0	40	72.7	86	66.7	313	73.1
Unsatisfactory:										
No improvement	15	9.6	12	13.8	10	18.2	23	17.8	66	15.4
Relapse	7	4.5	3	3.4	2	3.6	1	0.8	14	3.3
Progression of ocular condition	3	1.9	3	3.4	..	...	4	3.1	10	2.3
Counting fingers	1	0.6	1	1.1	1	1.8	4	3.1	7	1.6
Light perception	2	1.3	1	1.1	1	1.8	7	5.4	13	3.0
Blindness	..	...	..	...	1	1.8	4	3.1	5	1.2
Grand total	28	17.8	20	23.0	15	27.3	43	33.3	115	26.9

* The figures in this column refer to patients beginning treatment within two months of the onset of interstitial keratitis.

titis in the first eye were followed for more than two years; 13 of them were followed for more than five years. Only 2 of the 37 exhibited interstitial keratitis in the second eye. In both of these the involvement occurred in the two to five year period. These results confirm the original reports of Carvill and Derby [4] in which they stated that "inten-

4. Carvill, Maud, and Derby, G. S.: Interstitial Keratitis, Boston M. & S. J. **193**:403, 1925.

sive treatment when interstitial keratitis develops in one eye may have some influence in preventing the involvement of the second eye."

CLINICAL RESULTS OF TREATMENT OF INTERSTITIAL KERATITIS

There were 428 patients who were admitted with, or whose condition progressed to, interstitial keratitis in the total 1,010 patients with late prenatal syphilis forming the basis of this study. Of these 428 patients, 157 began treatment within two months of the onset. In 87 additional patients treatment was started later than in the first two months of the onset. Fifty-five patients were admitted with an active relapsing interstitial keratitis. In contrast with these, there were 129 patients for whom a diagnosis of interstitial keratitis was made on the basis of scars. In table 10 the advantage of early treatment of interstitial keratitis in the prevention of residual damage to the eye is shown.

The clinical results are reported in terms of restoration of vision to the affected eye.[5] The results of treatment for interstitial keratitis are reported as satisfactory unless there is a visual problem.

The patients with early acute involvement in the first attack of interstitial keratitis showed the highest proportion of excellent results —complete healing leaving the eyes clear with no corneal scars. This emphasizes the necessity for diagnosing, and starting treatment for, interstitial keratitis at the earliest possible moment. In few of the patients with interstitial keratitis who sought treatment for relapse or scars was it possible ultimately to obtain perfect vision with treatment. Interstitial keratitis did not terminate in blindness in a single one of the 157 patients who began treatment in the early acute stage, whereas it supervened in 4 who did not receive antisyphilitic treatment. However, even under the best therapeutic conditions certain patients respond poorly. Among the 157 patients treated in the early acute stage, 10 per cent were unimproved and 6.4 per cent showed relapse or progression. In the cases of the late acute stage and in those in which relapse

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5. The definition of terms used in evaluating end-results of treatment of interstitial keratitis is as follows: 1. "Excellent results" indicates that in all cases cure was reported, the eyes being clear, or having no corneal scars. 2. "Good results" indicates that slight corneal scars were present but that vision was reported as good. 3. "Improvement" denotes that improvement was reported to have resulted from treatment but that no definite data were given. 4. "Arrest" refers to cases in which it was reported that an old interstitial keratitis had become quiescent and in which no visual problem was mentioned. 5. "No improvement" indicates that no improvement resulted from treatment, that no further data were given or that severe corneal scars remained. 6. "Counting fingers" indicates that there was a visual problem, that no further data were given and that the patient could hardly see. 7. (a) "Light perception"; (b) "blindness." 8. (a) Relapse of interstitial keratitis or development of the condition in the other eye. (b) Progression of interstitial keratitis.

occurred it was possible through antisyphilitic treatment to maintain good useful vision in 73 per cent of the patients, even though nearly twice as many remained unimproved or lost useful vision as in the group with early acute involvement. In 129 patients a previous interstitial keratitis had resolved without medical attention, leaving an amount of scarring sufficient to justify a diagnosis of interstitial keratitis. Subsequent antisyphilitic treatment either resulted in some improvement in vision or prevented progression or relapse in 67 per cent of these patients. That a patient should not be allowed to go through interstitial keratitis without antisyphilitic therapy is evidenced by the fact that 12 per cent of the 129 patients lost useful vision because of lack of treatment. The institution of modern therapy in the early acute stage in the first attack decreased the incidence from 12 to 2 per cent among the 157 patients treated.

COMPARATIVE VALUE OF DRUGS IN THE TREATMENT OF INTERSTITIAL KERATITIS

The material studied definitely indicates that early treatment is essential in cases of interstitial keratitis to prevent involvement of the second eye and to protect from severe scarring. Although the acute stage of interstitial keratitis usually responds to the first few injections of arsphenamine and to treatment with a heavy metal, it is essential to administer adequate treatment (more than fifteen injections of arsphenamine and an appropriate amount of treatment with a heavy metal) in order to prevent a recurrence of the ocular condition. In patients so treated not a single relapse occurred. In patients in whom treatment for interstitial keratitis was delayed, satisfactory results were even more dependent on adequate therapy, as shown in table 11. The advantage of prolonging treatment after the eyes have cleared has been pointed out in a previous report, by Guy.[6] Old arsphenamine and neoarsphenamine appeared equally satisfactory in the treatment of interstitial keratitis.

The limited material does not permit any conclusive statement as to the effectiveness of supplemental fever and foreign protein therapy[7] combined with routine treatment. Patients with early interstitial keratitis treated with routine methods plus fever and foreign protein therapy failed to show as good results as those treated with routine therapy alone. However, in patients treated for chronic, relapsing or inactive interstitial keratitis, it appears from the limited material available that

6. Guy, W. H.: Interstitial Keratitis in Congenital Syphilis: Clinical Notes on Incidence and Treatment, J. A. M. A. **87**:1551-1555 (Nov. 6) 1926.

7. By foreign protein treatment is meant intramuscular injection of boiled milk or intravenous injection of typhoid paratyphoid vaccine in ascending doses.

the greatest success was obtained with adequate chemotherapy supplemented by fever and foreign protein treatment. The percentage of satisfactory results increased from 71 per cent with routine therapy to 88 per cent when fever and foreign protein therapy also were used.

When iodides are used as adjunct treatment for early acute interstitial keratitis the results are less satisfactory than if iodides are not given. It is possible that iodism in patients with acute interstitial keratitis has a tendency to aggravate the acute inflammatory reaction already present. At any rate, 91 per cent of the patients had a satisfactory outcome when iodides were not used, as against 78 per cent when

TABLE 11.—*Effectiveness of Various Drugs in the Treatment of Interstitial Keratitis*

	Stage of Interstitial Keratitis at Which Treatment Was Begun									
	Acute					Chronic, Relapsing or Inactive				
	Clinical Results of Treatment					Clinical Results of Treatment				
	Satisfactory		Unsatisfactory			Satisfactory		Unsatisfactory		
Kind of Treatment from Onset of Interstitial Keratitis	Number	Percentage	Number	Percentage	Total Number	Number	Percentage	Number	Percentage	Total Number
Arsphenamine-Heavy Metal										
Little* - Little	16	80.0	4	20.0	20	28	63.6	16	36.4	44
Little - Much	10	76.9	3	23.1	13	16	61.5	10	38.5	26
Much - Little	26	89.7	3	10.3	29	33	64.7	18	35.3	51
Much - Much	78	83.9	15	16.1	23	115	77.7	33	22.3	148
Routine therapy alone	106	86.1	17	13.8	123	155	71.4	62	28.6	217
Routine therapy with fever and foreign protein therapy	18	78.3	5	21.7	23	22	88.0	3	12.0	25
Iodides in conjunction with other types of therapy										
Iodides	68	78.2	19	21.8	87	128	76.6	39	23.4	167
No iodides	62	91.2	6	8.8	68	65	62.5	39	37.5	104
Heavy metal in conjunction with other types of therapy										
Bismuth	45	84.9	8	15.1	53	69	71.9	27	28.1	96
Mercury	77	82.8	16	17.2	93	114	72.6	43	27.4	157

* Little arsphenamine means from 1 to 15 injections; much arsphenamine, 16 or more injections. Little heavy metal means from 1 to 30 injections or weeks of mercury rubs, much, 30 or more injections or weeks of mercury rubs.

they were used. Of patients with chronic interstitial keratitis, a satisfactory result was achieved with iodides in 77 per cent, as contrasted with 63 per cent, the incidence when iodides were not used. Iodides, as has been pointed out by Guy,[6] are useful in resolving granulomatous tissue; this probably explains their especial value in the treatment of chronic interstitial keratitis. There did not appear to be any difference in the efficacy of heavy metals for treatment of interstitial keratitis. Equally good results were obtained with mercury and with bismuth.

SCHEME OF TREATMENT TO BE USED IN INTERSTITIAL KERATITIS

The best results were obtained in acute interstitial keratitis with the continuous scheme of treatment. Of 40 patients with acute involve-

ment treated continuously, 93 per cent had a satisfactory result, as compared with 77 per cent of the 69 on whom the intermittent scheme of treatment was followed. Apparently, keeping the local inflammatory reaction of the eye under constant attack from either arsenical or heavy metal serves a useful purpose in the acute stage. The chronic or inactive type of the disease may be compared to a late cutaneous indolent manifestation of syphilis. There are not so many specific changes as in cases in which chronic tissue reactions are present. In those cases the use of potassium iodide and intermittent administration of arsenical and heavy metals combined with nonspecific therapy give good results.

Results obtained in the cooperating clinics in the treatment of interstitial keratitis may be summarized as follows: In the acute stage of the disease adequate arsenical and heavy metal therapy given according to the continuous scheme and not accompanied by administration of

TABLE 12.—*Comparative Effectiveness of Continuous and Intermittent Schemes of Treatment After Detection of Interstitial Keratitis*

	Stage of Interstitial Keratitis at Which Treatment Was Begun									
	Acute					Chronic, Relapsing or Inactive				
	Clinical Results of Treatment					Clinical Results of Treatment				
	Satisfactory		Unsatisfactory			Satisfactory		Unsatisfactory		
Scheme of Treatment	Number	Percentage	Number	Per cent, age	Total Number	Number	Percentage	Number	Percentage	Total Number
Continuous	37	92.5	3	7.5	40	53	72.6	20	27.4	73
Intermittent	53	76.8	16	23.2	69	79	79.8	20	20.2	99

iodides or by fever and foreign protein treatment gave the highest percentage of satisfactory results. However, when the condition was of a chronic or relapsing type it was found preferable to supplement routine therapy with administration of potassium iodide internally and for the more resistant patients to use fever and foreign protein treatment as supplements. In this late stage of the disease it was found that rest periods between courses of arsenicals and heavy metals do no harm.

EFFECT OF RELAPSE IN INTERSTITIAL KERATITIS ON ULTIMATE OUTCOME

For purposes of this study, the definition of relapse as given by Carvill and Derby is used.[4] A relapse is a recurrence of the attack of inflammation occurring one year or more after the subsidence of the acute symptoms of the primary attack of interstitial keratitis. Relapse is one of the most serious problems in the care of interstitial keratitis. Of 149 patients with early acute involvement in whom the ultimate

outcome was known, 31 (21 per cent) experienced one or more relapses during observation or treatment. The satisfactory clinical outcome dropped from 86 to 71 per cent when a relapse occurred during the treatment of a patient with acute interstitial keratitis. Therefore, it is essential to avoid relapse. This can best be accomplished by continuous adequate treatment given in the early acute stage. Fifteen per cent of the patients so treated suffered a relapse, as contrasted with 29 per cent who were irregularly treated in the early acute stage of interstitial keratitis. The best means of avoiding either the occurrence or the relapse of interstitial keratitis is to treat adequately every patient with prenatal syphilis while the disease is still latent in order to prevent the development of this ocular condition.

CONCLUSIONS

A report is made by the Cooperative Clinical Group from a survey of 1,010 cases of late prenatal syphilis, the patients being under observation or treatment for two years or more. All these patients were at least 2 years of age when they were admitted to the clinic. Less than 2 per cent of the patients had received antisyphilitic treatment in infancy.

Interstitial keratitis was found in approximately one third of the cases. In 39 per cent the condition was latent when the patient was admitted.

In general, the outlook for a satisfactory clinical outcome decreased if the treatment was delayed until after the manifestation either had become chronic or had healed spontaneously leaving residual scars.

A fixed positive serologic reaction of the blood in patients with early acute prenatal syphilis lessened the favorable outlook while in those with latent prenatal syphilis it seemed to have little bearing on the outcome.

Patients under observation and treatment before the age of 15 showed a better clinical response than older patients.

Patients who were adequately treated for more than a year had a higher proportion of satisfactory clinical results (62 per cent) than those treated for a shorter period (49 per cent).

A patient with late prenatal syphilis is continuously subject to risk of interstitial keratitis up to 25 years of age unless he is given adequate antisyphilitic treatment, which consists of at least sixteen injections of an arsenical and thirty-one injections, or weeks of rub, of heavy metal.

The best prophylactic treatment for interstitial keratitis is the use of adequate continuous therapy for all patients with latent prenatal syphilis, for 90 per cent of the patients with interstitial keratitis had been untreated before the first attack. Thirty-six per cent of untreated

patients with prenatal syphilis exhibited interstitial keratitis, in contrast with 2 per cent of the patients who had received modern antisyphilitic treatment.

Involvement of the second eye in patients with interstitial keratitis is a complication greatly to be feared. Even when the first eye is treated early the other eye may become involved, and under such conditions, 87 per cent of the patients will show extension within two years' time.

The successful prevention of involvement of the second eye in patients with interstitial keratitis consists in early adequate treatment of syphilis at the time of involvement of the first eye. Of patients treated within six months of the onset of interstitial keratitis in the first eye, the involvement remained unilateral in 71 per cent. The patient with acute interstitial keratitis should not be allowed to go through his attack without adequate antisyphilitic treatment. It was found that six times as many untreated as treated patients lost useful vision. In cases of chronic and relapsing interstitial keratitis, administration of iodides and fever and foreign protein therapy were found to be valuable adjuncts. This was not so in the cases of early acute involvement. In those cases adequate arsenical and heavy metal therapy, consisting of at least fifteen injections of an arsenical and of appropriate heavy metal given by a continuous scheme, gave excellent results (93 per cent).

Prof. H. J. Gerstenberger gave permission to use some of the material on prenatal syphilis from his pediatric clinic at the Western Reserve University.

SYPHILOTOXEMIA IN THE NEW-BORN

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Many controversies exist regarding an accurate basis for the diagnosis of syphilis in the new-born. Certain investigators contend that the diagnosis is warranted only when clinical symptoms appear, while others accept at face value a positive or negative serologic reaction of the blood of the mother, of that of the new-born or that of both as the deciding factor. Men especially trained in syphilis will no doubt recognize physical signs when they occur. However, in a survey of the literature by Cruickshank [1] and in our own experience clinical symptoms do not occur with sufficient constancy to allow the disease to be recognized in more than a small percentage of the infected infants. On the other hand, diagnosis which is grounded solely on a positive serologic reaction, particularly on that of the mother's and often on that of the infant's blood, will carry into this disease category a higher percentage of infants than rightfully belong there.

In this paper we shall review the literature on the latter point, and present observations on a group of infants who had positive reactions of the blood from the cord or from that of the jugular vein within the early neonatal period but whose blood was shown by follow-up observation to become and remain negative. This clinical study is proposed as an additional evidence in support of the suggestion already made by one of us [2] before this body, namely, that ". . . the positive serums of the mother may pass to the child without the organism having done so." Thus we identify ourselves with clinicians who believe that the course for the diagnosis of syphilis in these infants lies in the

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This paper is a part of a symposium on syphilis presented at the annual meeting of the American Dermatological Association. The discussion on the symposium follows the article by Drs. Dennie and Miller, p. 591.

1. Cruickshank, J. N.: Maternal Syphilis as a Cause of Death of the Foetus and of the New-Born Child, Medical Research Council, Special Report Series, no 82, London, His Majesty's Stationery Office, 1924, p. 19.

2. Cregor, F. W.: The Relationship of the Serology of the Blood to That of the Spinal Fluid in Congenital Syphilis, Arch. Dermat. & Syph. **24**:733 (Nov.) 1931.

proper correlation of the clinical signs, the various laboratory procedures and the anamnestic evidence.

REVIEW OF THE LITERATURE

During the past quarter of a century numerous opinions have been advanced concerning the value of a Wassermann test made on the new-born at, or within the few days or weeks following, birth. Most writers seem agreed that a negative Wassermann reaction in a child born of a syphilitic mother is inconclusive and does not necessarily rule out the presence of the disease. However, on the basis of interpretation of an early positive reaction of the blood from the cord or from a vein, they seem to divide into two rather distinct schools of thought. The one regards a positive result as a definite evidence of infection in the child,[3] while the other considers it as inconclusive or merely as a sign indicating the necessity of a continued intensive study of the infant.[4]

3. (*a*) Couvelaire: Rev. mens. de gynéc., d'obst. et de pédiat. **6**:70, 1911. (*b*) Klaften, E.: Arch. f. Gynäk. **134**:88, 1928. (*c*) Klee, F., and Hofmann, E.: Monatschr. f. Geburtsh. u. Gynäk. **62**:21, 1923. (*d*) Kruckenberg, R.: Ztschr. f. Geburtsh. u. Gynäk. **74**:451, 1913. (*e*) McCord, J. R.: Syphilis and Pregnancy, J. A. M. A. **105**:89 (July 13) 1935. (*f*) Pfaundler: München. med. Wchnschr. **45**:127, 1918. (*g*) Steinert, E., and Flusser, E.: Arch. f. Kinderh. **65**:45, 1915. (*h*) Wile, U. J., and Shaw, J. W.: The Prenatal Treatment of Syphilis, J. A. M. A. **95**:1791 (Dec. 13) 1930. (*i*) Belding, D. L.: Am. J. Syph. **9**:132 ,1925.

4. (*a*) Brunner, K.: Monatschr. f. Geburtsh. u. Gynäk. **57**:42, 1922. (*b*) Dunham, E. C.: The Diagnosis of Congenital Syphilis in the New-Born, Am. J. Dis. Child. **43**:317 (Feb.) 1932. (*c*) Duzár, J.: Monatschr. f. Kinderh. **27**:222, 1923. (*d*) Esch, P.: Arch. f. Gynäk. **117**:147, 1922. (*e*) Fildes, P.: Report of the Local Governing Board upon the Prevalence of Congenital Syphilis Among the Newly-Born of the East End of London, London, T. F. Unwin, 1915. (*f*) Fischl, R.: Monatschr. f. Kinderh. **25**:110, 1923. (*g*) Handorn, L., and Georgi, F.: Zentralbl. f. Gynäk. **62**:898, 1923. (*h*) Ingraham, N. R., Jr.: Am. J. Syph. & Neurol. **19**:547, 1935. (*i*) Jeans, P. C., and Cooke, J. V.: Am. J. Syph. **6**: 569 (Oct.) 1922. (*j*) Kilduffe, R.: Am. J. M. Sc. **164**:677, 1922. (*k*) Kolmer, J.: Standardization of the Wassermann Reaction, J. A. M. A. **77**:776 (Sept. 3) 1921. (*l*) Lange, R.: Jahrb. f. Kinderh. **90**:83, 1919. (*m*) Lemež, L.: Ztschr. f. Kinderh. **48**:97, 1929. (*n*) Lesser, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 19, p. 287. (*o*) Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933. (*p*) Pankow: Arch. f. Gynäk. **120**:125, 1923. (*q*) Parmelee, A. H., and Halpern, L. J.: The Diagnosis of Congenital Syphilis, J. A. M. A. **105**:563 (Aug. 24) 1935. (*r*) Pomini, F.: Ann. di ostet. **44**:688, 1922. (*s*) Rietschel, H.: Ergebn. d. inn. Med. u. Kinderh. **12**:160, 1913. (*t*) Roux, E.: La réaction de Wassermann chez le nouveau-né et le nourrisson, Thèse de Montpellier, no. 59, 1913; Ztschr. f. Kinderh. **8**:364, 1914. (*u*) Thomsen, O., and Boas, H.: Arch. f. Dermat. u. Syph. **111**:91, 1912. (*v*) Willenbücher, F.: Arch. f. Gynäk. **116**: 558, 1923. (*w*) Williams, J. W.: Bull. Johns Hopkins Hosp. **31**:335, 1920. (*x*) Yerington, H. H.: Arch. Pediat. **35**:40, 1918. (*y*) Cruickshank.[1] (*z*) Belding.[3i]

Certain observers of the first group admit that they have noted these positive reactions, which may shortly and of themselves reverse to negative, but they still maintain that infants who exhibit those reactions are infected.[5] Others of the second group do not fully reject the idea of this reversal phenomenon being a positive sign of a latent syphilitic infection.[6] To explain this seemingly pseudopositive reaction of the blood of some infants, various theories have arisen. While some observers have expressed the belief that these reaction-producing substances may be transferred while the fetus is still in utero, others have felt that the transfer results probably during the increased pressures produced with labor or takes place through probable structural breaks of the placenta at its detachment. Certain workers have been content to class these transmitted substances under the broader term of reagins or antibodies,[7] while others have attempted to place their fingers on a more definite etiologic substance. Willenbücher [4v] theorized that the pathogenic and nonpathogenic organisms, which are normal inhabitants of the vagina, are at the time of delivery pressed through the mucous membrane of the walls of this structure into the blood stream of the mother and that antibodies to these organisms are formed there, passing to the infant's blood. It is needless to say that owing to the short period he would allow for the completion of such a process and the high degree of theory of such a belief, this idea has not been generally accepted.

Cooke [8] expressed the belief that complement-fixing substances present in the mother's serum may be transmitted to her offspring and persist in the infant's blood for a certain number of weeks, though they disappear usually by the end of the second and always by the end of the third month. Jeans and Cooke [4l] concluded that these complement-fixing substances can be transmitted to the child without actual transference of the infection. In line with this same thought, Rietschel [4s] stated that since such a process is a passive transfer these substances will after some time be excreted and that therefore a true transfer of the disease has not occurred.

Lemež [4m] concurred in the opinion of Duzár [4c] that during gestation the mother's blood shows an increased serum lability due to the increase of globulin and that this is a probable explanation of this finding. In addition, Lemež [4m] cited as a likewise possible interpretation in this con-

5. Pfaundler.[3f] Steinert and Flusser.[3g]

6. Cruickshank.[1] Brunner.[4a] Lesser.[4n] Pankow.[4p] Rietschel.[4s] Thomsen and Boas.[4u]

7. Cruickshank.[1] Pfaundler.[3f] Dunham.[4b] Fildes.[4e] Moore.[4o] Pankow.[4p] Thomsen and Boas.[4u]

8. Cooke, J. V.: Am. Rev. Tuberc. **6**:127 (April) 1922.

dition the suggestion advanced by Mayerhofer and his co-worker [9] in respect to the underlying cause of erythema toxicum neonatorum, namely, that albumins or albuminous toxins may be transferred to the child and call forth allergic reactions.

Esch,[4d] Pankow [4p] and Pomini [4r] expressed the belief that these pseudopositive reactions are probably due to lipoidal substances originating in the mother's blood or in the placental tissue and entering the infant's circulation at, or prior to, birth.

The question has been raised as to whether this process occurs in consequence of an entrance into the child's circulation during birth [4g] of juices from the placenta or cord tissue or of amniotic fluid. Kruckenberg [3d] investigated this idea and concluded that these substances were of but slight or no importance in the production of a positive Wassermann reaction.

Most observers agree that only the reaction which has reversed to negative by the tenth or fourteenth day of life can be regarded as pseudopositive and that a continuance of a positive serologic reaction beyond that time is an evidence of true infection in the child.[10] However, if Cooke [8] is right in stating that these complement-fixing substances may remain in the infant's blood up to the end of the second or third month, then it would seem possible that in some instances a pseudopositive reaction could occur even beyond the second week. Since the concentration of these substances in the serum is thought to decrease in the postdelivery period, we see a possible reason for the gradual reduction in the degree of positivity which is sometimes recorded. Lemež [4m] reported that the highest percentage of positive reactions occur in the first twenty-four hours and on the first, second, fourth and eighth days of neonatal life and that in the majority of cases these pseudopositive reactions have become negative by the third to the fifth day.

GENERAL CLINICAL CONSIDERATIONS

Our present study concerns itself only with infants who showed a positive serologic reaction of the blood at birth which early and without treatment reversed to negative. Such a finding we regard as an evidence of the transference from the syphilitic mother of a syphilotoxemia rather than of a true infection.

As an introduction to the consideration on infants of this group it becomes necessary to digress momentarily to a consideration of the entire series of infants born of syphilitic mothers. However, since no

9. Mayerhofer, E., and Lypolt-Krajnovic, M.: Ztschr. f. Kinderh. **43**:630, 1927.

10. Dunham,[4b] Jeans and Cooke,[4i] Lemež,[4m] Lesser,[4n] Moore,[4o] Roux,[4t] Yerington.[4x]

discussion on the condition in these infants can be complete without an evaluation of the mothers' condition we present in table 1 an analysis of observations on sixty-five syphilitic mothers who made up the total series. Although we are not at this time concerned with any detailed evaluation of this total series, the exceedingly low incidences, 2.03 per cent, in the total deliveries of an indigent clientele, deserves comment. In six other reports studied [11] this incidence showed a range of from 3.6 to 15.8

TABLE 1.—*Relation of Total Deliveries to Deliveries of Syphilitic Mothers in the William Coleman Hospital of Indiana University from Aug. 8, 1932, to Dec. 15, 1935*

	Number	Percentage
1. Total deliveries	3,196	
2. Deliveries of syphilitic mothers	65	2.03
a. Parity		
Primipara	23	35.38
Multipara	42	64.62
b. Single or multiple pregnancy		
Single	64	98.46
Twins	1	1.54
c. Type of mother's disease		
Congenital	16	24.62
Acquired	42	64.61
Undetermined	7	10.77
(1) Stage of congenital disease		
Latent	14	21.54
Late	2	3.08
(2) Stage of acquired disease		
Early	7	10.77
Early latent, latent or late	35	53.84
d. Disease treated or untreated		
(1) Treated both before and during pregnancy	28	43.08
(2) Treated only during pregnancy	32	49.08
(3) No treatment at any time	5	7.69
e. Serologic reactions of blood during pregnancy *		
(1) Wassermann		
Positive	44	67.07
Questionable	6	9.23
Negative	15	23.08
(2) Kahn		
Positive	45	69.22
Questionable	11	16.92
Negative	9	13.84
(3) Kline		
Positive	48	73.85
Questionable	9	13.85
Negative	8	12.30

* Positive reaction means 4 or 3 plus reactions; questionable, 2 or 1 plus reactions; negative, frankly negative reactions.

per cent, with an average of 8.3 per cent. However, the low percentage in our series can probably be explained by the fact that the William Coleman Hospital accepts only white women, who come chiefly from suburban or rural sections. The high percentage of infants born alive is particularly noteworthy. Furthermore, in the group still under

11. Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Stokes, J. H.; Wile, U. J.; Clark, T.; Parran, T.; Vonderlehr, R. A., and Usilton, L. J.: Ven. Dis. Inform. **15**:83 (March) 1934. Gammeltoft, S. A.: Am. J. Obst. & Gynec. **15**:747, 1928. Sänger: Monatschr. f. Geburtsh. u. Gynäk. **46**:5, 1917. Wagner, G. A.: Arch. f. Gynäk. **120**:133, 1923. Cruickshank.[1]

observation, we find that approximately 91 per cent have shown no definite evidence of syphilis. However, the fact that 92.31 per cent of the total number of syphilitic mothers received some treatment is regarded as a probable cause for this apparently good result. Furthermore, it should be recalled that in addition to the fact that they received this treatment, 78.5 per cent of these mothers had either congenital or a latent or late stage of acquired syphilis. These results parallel rather

TABLE 2.—*Analysis of Observations on All Infants Born of Syphilitic Mothers at the William Coleman Hospital of Indiana University from Aug. 8, 1932, to Dec. 15, 1935*

	Number	Percentage
Number of infants born of syphilitic mothers	66	
A. Infants born alive	60	90.90
1. Still living and under observation	32	48.48
a. Syphilitic, under treatment (age 8, 14 and 15 months)	3	4.55
b. Nonsyphilitic, untreated	29	43.94
(1) Negative reaction from birth (age 5, 10, 12, 13, 13, 21 and 32 months)	7	10.61
(2) Positive Wassermann at birth with early reversal (age 8-42 months, average age 22.8 months)	22	33.33
2. Died in neonatal or early infancy period	5	7.58
a. Death believed due to syphilis (age 1 hour, 19, 34 and 38 days)	4	6.06
b. Death believed not due to syphilis (age, 3 months, streptococcic meningitis)	1	1.52
3. Fully or partly unaccounted for	23	34.85
a. Observed partially (serologic tests)	5	7.58
(1) Negative (age 6 weeks, 4, 10, 11 and 13 months)	5	7.58
b. Not observed since tenth day	18	27.27
(1) Believed syphilitic	3	4.55
(2) Believed nonsyphilitic	13	19.69
(3) Not determined	2	3.03
B. Infants born dead	6	9.09
1. Under term	3	4.55
a. Believed syphilitic (delivered at 6 and 8 months)	2	3.03
b. Believed nonsyphilitic (delivered at 6 months; hysterectomy due to placenta praevia)	1	1.52
2. At term	3	4.55
a. Macerated	1	1.52
(1) Believed syphilitic	1	1.52
b. Nonmacerated	2	3.03
(1) Believed syphilitic	1	1.52
(2) Believed nonsyphilitic	1	1.52

closely those in the treated group reported by McKelvey and Turner,[12] of the clinic of the Johns Hopkins Hospital. At this point we should like to make another observation. We feel that proper attention has not been given in most reports to whether the mother's disease was acquired or congenital, and we feel that it is of great prognostic value to the offspring if it can be established that the mother's disease is inherited.

12. McKelvey, J. L., and Turner, T. B.: An Analysis of the Outcome of Pregnancy in Relation to Treatment in Nine Hundred and Forty Cases, J. A. M. A. **102**:503 (Feb. 17) 1934.

Table 3 shows the available results of the examinations of the blood made on all infants. We were impressed both with the high percentage of positive results of the Wassermann in relation to those of the Kahn or of the Kline test and by the high incidence of negative results of the Kahn or of the Kline as compared to those of the Wassermann test. We were unable to explain this phenomenon, and for that reason we sought the opinion of Dr. Culbertson, of our university laboratories,

TABLE 3.—*Analysis of Results of Serologic Tests of the Blood of All Infants Born of Syphilitic Mothers at the William Coleman Hospital of Indiana University from Aug. 8, 1932, to Dec. 15, 1935*

	Positive*	Questionable*	Negative*	Unchecked
Blood from the cord only: 27 cases (40.19%)				
Wassermann reaction	19 (28.79%)	1 (1.52%)	7 (10.61%)	.....
Kahn reaction	4 (6.06%)	5 (7.58%)	18 (27.27%)	.....
Kline reaction	4 (6.06%)	4 (6.06%)	19 (28.79%)	.....
Blood from the jugular vein only: 3 cases (4.55%) (within first ten days)				
Wassermann reaction	2 (3.03%)	.....	1 (1.52%)	.....
Kahn reaction	1 (1.52%)	1 (1.52%)	.....	1 (1.52%)
Kline reaction	1 (1.52%)	1 (1.52%)	1 (1.52%)	.....
Blood from the cord and from the jugular vein, 23 cases (34.85%)				
Blood from the cord				
Wassermann reaction	15 (22.73%)	1 (1.52%)	7 (10.61%)	.....
Kahn reaction	6 (9.09%)	2 (3.03%)	15 (22.73%)	.....
Kline reaction	5 (7.58%)	1 (1.52%)	17 (25.76%)	.....
Blood from the jugular vein (within first ten days)				
Wassermann reaction	14 (21.21%)	2 (3.03%)	7 (10.61%)	.....
Kahn reaction	5 (7.58%)	2 (3.03%)	12 (18.18%)	4 (6.06%)
Kline reaction	5 (7.58%)	.....	17 (25.76%)	1 (1.52%)
Wassermann reaction not checked with either blood from the cord or from the jugular vein within first 10 days)				13 (19.69%)
Total tests on blood from the cord: 50 (75.73%)				
Wassermann reaction	34 (51.52%)	2 (3.03%)	14 (31.22%)	16 (24.24%)
Kahn reaction	10 (15.15%)	7 (10.61%)	33 (50.00%)	16 (24.24%)
Kline reaction	9 (13.64%)	5 (7.58%)	36 (54.54%)	16 (24.24%)
Total tests on blood from the jugular vein: 26 (39.39%) (within first ten days)				
Wassermann reaction	16 (24.24%)	2 (3.03%)	8 (12.15%)	40 (60.60%)
Kahn reaction	6 (9.09%)	3 (4.55%)	12 (18.18%)	45 (68.18%)
Kline reaction	6 (9.09%)	1 (1.52%)	18 (27.27%)	41 (61.12%)

* Positive reaction means 4 or 3 plus; questionable, 2 or 1 plus; negative, frankly minus.

who stated that he has the feeling that there may be different substances producing the Kline and Kahn reactions or that different morphology of the same substance may explain the discrepancy.

CONSIDERATION ON THE SYPHILOTOXEMIA GROUP

Table 4 summarizes the observations on twenty-two infants constituting the syphilotoxemia group and on their mothers.

In evaluating the condition of any child born of a syphilitic mother several factors of the maternal history must be taken into consideration. There are observers who believe that repeated pregnancies tend eventually

toward the production of a nonsyphilitic infant. Since factors both of duration of disease and of treatment in mothers entered into our series, we were unable to determine definitely the influence exerted by previous pregnancies in producing these apparently normal children. However, we believe that the two factors—that of the lateness of the disease in these mothers and that of the treatment they received—contributed greatly to the condition of their offspring.

The final and last step of our considerations deals with the infants of the syphilotoxemia group, as given in table 5. We believe that syph-

TABLE 4.—*Analysis of the Group of Syphilitic Mothers Who Gave Birth to Infants of the Syphilotoxemia Group*

	Number	Percentage
1. Total number of syphilitic mothers	65	
2. Syphilitic mothers giving birth to child with syphilotoxemia	22	33.85
a. Parity		
Primipara	7	31.82
Multipara	15	68.18
b. Single or multiple pregnancy: single	22	100.00
c. Type of mother's disease		
Congenital	4	18.18
Acquired	17	77.25
Undetermined	1	4.54
(1) Stage of congenital disease		
Latent	2	9.09
Late	2	9.09
(2) Stage of acquired disease: early latent; latent, and late	17	77.25
d. Disease treated or untreated		
(1) Treated both before and during pregnancy	11	50.00
(2) Treated only during pregnancy	11	50.00
e. Serologic reactions of the blood during pregnancy		
(1) Wassermann reaction		
Positive	17	77.27
Questionable	3	13.64
Negative	2	9.09
(2) Kahn reaction		
Positive	18	81.82
Questionable	2	9.09
Negative	2	9.09
(3) Kline reaction		
Positive	20	90.91
Questionable	0	00.00
Negative	2	9.09

ilis and tuberculosis (although resulting from wholly dissimilar organisms) are comparable in their invasion of the body. While the consensus is that tuberculosis is not transmitted directly from mother to child (unless it is through the skin in the process of birth) and that syphilis is often transmitted directly from mother to child in utero, it is a well known truism that nonsyphilitic children are often born of mothers known to be syphilitic. We believe that the dyscrasia which is recognized in the child born of a syphilitic mother is comparable to the well recognized tuberculous diathesis observed in the infants born of tuberculous mothers and that these conditions may result from a syphilitic or tuberculous toxemia occurring with greater or lesser

severity during the intra-uterine development of the child. Thus these children may show evidence of malnutrition or even changes in the bones resulting from toxemias occurring at the time these bone centers are erupting, and Cook's observation of the transference of complement-fixing bodies from the mother to the infant in both of these diseases is interesting.

As an example of this we observed an infant born of a mother proved to have congenital syphilis who had changes in the long bones disclosed by roentgenograms made when the child was 5 days and

TABLE 5.—*Analysis of Findings in Infants of the Syphilotoxemia Group*

1. Total number of infants born of syphilitic mothers				66
2. Infants belonging to the syphilotoxemia group				22 (33.33%)
a. Findings at birth or during hospital period				22 cases
(1) Serologic examination of the blood				
a. Cord, 21 cases	Positive	Questionable	Negative	Unchecked
1. Wassermann reaction	19 (86.36%)	1 (4.55%)	1 (4.55%)	1 (4.55%)
2. Kahn reaction	6 (27.27%)	3 (13.64%)	12 (54.55%)	1 (4.55%)
3. Kline reaction	4 (18.18%)	2 (9.09%)	15 (68.18%)	1 (4.55%)
b. Jugular vein (during first ten days), 12 cases (this group includes the 1 case in which blood from the cord was not tested)				
1. Wassermann reaction	11 (50.50%)	1 (4.55%)	0 (00.00%)	10 (45.45%)
2. Kahn reaction	4 (18.18%)	1 (4.55%)	7 (31.81%)	10 (45.45%)
3. Kline reaction	5 (22.73%)	0 (00.00%)	7 (31.81%)	10 (45.45%)
(2) Results of physical examinations	0 (00.00%)	.....	22 (100.00%)	.....
(3) Results of roentgen examination of long bones	0 (00.00%)	1 (4.55%)	10 (45.45%)	11 (50.00%)
b. Findings during observation (without treatment), 22 cases				
(1) Repeated serologic examinations of the blood (jugular or arm vein)				
a. Wassermann reaction	0 (00.00%)	0 (00.00%)	22 (100.00%)	
b. Kahn reaction	0 (00.00%)	0 (00.00%)	22 (100.00%)	
c. Kline reaction	0 (00.00%)	0 (00.00%)	22 (100.00%)	
(2) Results of repeated physical examinations	0 (00.00%)	.....	22 (100.00%)	
(3) Results of check of roentgen examination of long bones	0 (00.00%)	3 (13.64%)	19 (86.36%)	
c. Period of observation				
(1) Longest, 42 months				
(2) Shortest, 8 months				
Average for all, 22.8 months				

15 months old, respectively. This child showed a zone of osteochondritic rarefaction in both femurs, tibias and radii. There was also a nuclear sclerotic formation in one of the tarsal bones.

In the case of this patient and in those of the two other infants born of mothers with acquired syphilis who showed suggestive changes on roentgen examination we have withheld treatment because of (1) the lateness of the disease and its treatment in their mothers, and (2) the persistence of these children in failing to show any clinical or serologic signs of syphilis in the fifteenth, twelfth and eighth months of observation, respectively.

In this series, as in others reported, the unreliability of the Wassermann test on blood drawn early in life is noted. We also noted the high

percentage of positive results of the Wassermann as compared to those of the Kahn or of the Kline test and also the high percentage of negative results of the Kahn or of the Kline as compared to those of the Wassermann test.

In the infants observations on whom are reported here, as in the entire series still under observation, we failed to find a sign attributable to syphilis at any time in repeated physical examinations.

Even now certain physicians adhere to the old view, which placed all children born of syphilitic mothers on treatment, while others give therapy to all children showing a positive Wassermann reaction. Had we followed the first view, 91 per cent of the infants observed would have been needlessly exposed to the potential dangers of antisyphilitic medication. Had we been guided by the second plan, 69 per cent of these same infants would have been given unjustified therapy. Both views seem unfortunate, and, in line with the second view, we wish to call attention to the regrettable tendency of physicians in general to make the Wassermann reaction the sole basis for both the beginning and the ending of treatment. Over several years a basis for the diagnosis of acquired syphilis has been formulated, and it seems high time that some capable body undertake a study to bring the same order to the diagnosis of syphilis in this early period of life.

Pusey [13] cautioned several years ago that "Syphilis which develops in the fetus *in utero* has essential differences from infantile acquired syphilis and should be sharply distinguished from it." That statement and this presentation, we believe, indicate that syphilitic infants in the early period of life present both peculiar and individual problems in diagnosis.

CONCLUSIONS

1. The establishment of whether the mother's disease is acquired or congenital deserves greater attention than has been given it in the literature. The child born of a mother whose disease is congenital has a different prognosis than the one born of a mother whose disease is acquired.

2. Latency or late disease in the mother, especially when associated with antisyphilitic treatment given during, or during and prior to, the pregnancy appears to be of definite value in the production of a nonsyphilitic child.

3. The influence which previous pregnancies of the mother exert toward the begetting of a normal child could not be definitely established in this series.

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13. Pusey, W. A.: Principles and Practice of Dermatology, New York, D. Appleton & Co., 1917, p. 626.

4. A positive serologic reaction of the blood in the new-born infant may be only a manifestation of a syphilotoxemia rather than a demonstration of true syphilitic infection.

5. The percentage of positive results of the Wassermann test in the new-born infants observed does not correspond in any comparable way to the result of the Kahn or of the Kline test.

6. From our own experience, as well as from that of others, when a reversal of a positive Wassermann reaction occurs, it does so early, though it seems logically possible for a reaction to remain positive for a longer period than the usual ten to fourteen days recorded in the literature.

7. Various theories have been proposed to explain these pseudo-positive reactions, but so far the causation of this phenomenon is not determined.

8. It is evident from studies of the literature and from our own experience that some capable body should undertake to establish a more ordered plan for the diagnosis of syphilis in the new-born.

ARSPHENAMINE DERMATITIS

PARALYTIC ILEUS AND PERFORATION OF THE INTESTINE AFTER TREATMENT WITH ARSPHENAMINE

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Arsphenamine dermatitis is always feared as a complication in the intensive treatment of syphilis. Accidents of this type are comparatively rare, yet serious reactions present a therapeutic problem which all dermatologists hate to encounter.

Franklin,[1] citing Harrison, stated that there were 370 cases of mild and severe arsphenamine dermatitis occurring in a total of 39,377 treated syphilitic patients during the Great War, or an incidence of this type of complication of 0.9 per cent. Harrison admitted that this figure is probably a little higher than that found in private practice. The Milian syndrome was unknown at that time. It is estimated that the percentage of patients who exhibit arsphenamine dermatitis is between 0.5 and 0.9.

The percentage of deaths from arsphenamine dermatitis is surprisingly low. In Harrison's series of 370 patients, 18, or 5 per cent, died. This figure represents a fair average of the number of deaths noted by other investigators. From the literature Christianson [2] collected the autopsy reports in 72 cases of fatal arsphenamine dermatitis. His figures are extremely interesting and are presented here in the form of a table (our arrangement).

It will be noted from these figures that the destructive action of arsphenamine on the small blood vessels of the gastro-intestinal tract and brain constituted the most marked observations at autopsy. If to these one adds its unusual action on the hematopoietic system one can

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1. Franklin, John L.: Salvarsan Dermatitis, Brit. J. Dermat. **42**:165, 1930.

2. Christianson, O. O.: Arsenic Necrosis of the Stomach After Intravenous Injection of Neoarsphenamine, Arch. Path. **20**:891 (Dec.) 1935.

easily see that death is primarily due to the adverse action of the arsenic on the vascular system and hematopoietic organs.

Petrie [3] stated that hemorrhages in different parts of the body are the most common observation at autopsy in cases of fatal arsphenamine poisoning.

Many authors have noted the occurrence of fatal and nonfatal multiple hemorrhages of the skin and mucous membrane. Smith,[4] O'Leary and Conner,[5] Combes,[6] Stokes [7] and Moore [8] have noted reactions of this nature. We have noted several instances of hemorrhage of the skin in cases of severe arsenical dermatitis. In one case the palms and soles were lifted from their foundations by pools of laked blood.

Autopsy Reports Collected from the Literature (1917-1933) by Christianson

	Number of Cases
Total number of cases	72
Diagnosis	
Aplastic anemia	14
Agranulocytosis	7
Purpura haemorrhagica	4
Acute yellow atrophy	4
Necrosis of, and hemorrhages in, the kidneys	2
Hemorrhagic encephalitis	18
Arsenic poisoning without intestinal changes	25
Observations on the stomach and intestines	
No change	38
Petechial hemorrhages	23
Hemorrhages in the stomach alone	8
Hemorrhages in the small bowel	2

Others (Wilkinson and Dodd,[9] Jacquelin, Célice and Langlois,[10] Osborne [11]) have noted the effect of arsphenamine on the hematopoietic system.

3. Petrie, E., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930.

4. Smith, C. Morton: Severe Bleeding and Purpura Following the Administration of Neoarsphenamine, Arch. Dermat. & Syph. **11**:237 (Feb.) 1925.

5. O'Leary, Paul A., and Conner, H. Milton: Am. J. Syph. **9**:262, 1925.

6. Combes, F. C., Jr.: Purpura Hemorrhagica Following Sulpharsphenamine, Arch. Dermat. & Syph. **15**:194 (Feb.) 1927.

7. Stokes, John H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934.

8. Moore, Joseph E.: Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

9. Wilkinson, S. J., and Dodd, K.: Severe Granulocytic Aplasia of the Bone Marrow, J. A. M. A. **90**:663 (March 3) 1928.

10. Jacquelin, A.; Célice, J., and Langlois: Post-arsenobenzole agranulocytosis, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:8 (Jan. 21) 1929.

11. Osborne, Earle D.: Microchemical Studies of Arsenic in Arsenical Dermatitis, Arch. Dermat. & Syph. **12**:773 (Dec.) 1925; **18**:37 (July) 1928.

The general pathologic manifestations in cases of reactions of this type may be divided into the following groups:

(a) Exfoliating dermatitis in which the deposit of arsenic is noted in the sweat glands, oil glands, hair follicles and hair shafts and only slightly in the epidermis (Osborne).

(b) Hemorrhagic changes, in cases of which, according to Christianson, the ". . . walls of the small arterioles stain poorly and the endothelial cells of many were swollen and loosened from the wall of the vessel." These same changes were observed in the vessels of the brain in cases of hemorrhagic encephalitis, extravasated blood being observed in the surrounding tissue. There may even be hemorrhages in the wall of the vena cava itself, as noted by Christianson. Small veins and arterioles as well as capillaries are often thrombosed, producing not only hemorrhages but necrosis of tissue when vessels other than capillaries are involved. The liver often shows central necrosis of the lobulus, fatty degeneration of the cells and numerous small hemorrhages into its substances. The spleen often discloses the same pathologic changes, and in addition infarcts of various sizes may be present. The intestines are often affected. One of us (C. C. D.) has observed flakes of intestinal mucosa in the stools of patients with asphenamine dermatitis. In one instance intestinal casts of mucous membrane from 2 to 3 inches (5 to 7.6 cm.) long were discovered in the feces.

Christianson concluded that arsenic does not act directly on the stomach and intestinal mucosa but acts indirectly by affecting the blood supply. He held the opinion that the destruction is secondary to vasoparalysis and cited the work of Pistorius [12] and of Unterberger and Boehm [13] to confirm his assertion.

The bone marrow often becomes pale, owing to fatty degeneration, which is a common observation in cases of agranulocytosis due to arsphenamine.

The kidneys often show marked changes ranging from edema and cloudy swelling to destruction of the renal substance. Hemorrhagic nephritis is sometimes seen. That hemorrhage occurs in the kidneys in cases of nonfatal arsphenamine dermatitis is shown by the fact that red blood cells are nearly always present in the urine of patients with this condition.

Edema of the brain and spinal cord is nearly always present even if there are no multiple hemorrhages.

We wish to report 2 cases of arsphenamine dermatitis; in 1 of these death was due to adynamic paralytic ileus with perforation of the large bowel.

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12. Pistorius, Hugo: Arch. f. exper. Path. u. Pharmakol. **16**:188, 1882.
13. Unterberger and Boehm: Arch. f. exper. Path. u. Pharmakol. **2**:89, 1874.

We believe that the perforation of the intestine was due primarily to involvement of the vessels of the intestinal wall. The preceding citations from the literature show that hemorrhages in the lining of the stomach and intestines are not uncommon.

Black [14] reported a case in which multiple hemorrhages occurred throughout the entire gastro-intestinal tract.

Phelps [15] held the same view.

We believe the explanation of our cases to be as follows: The neoarsphenamine or some of its side-products injured the blood vessels to such an extent that they were thrombosed, localized necrosis of the intestinal wall resulting. In addition, there might have occurred a paradoxical therapeutic result of such intensity that the endothelium, in response to the physiologic stimulation, left the wall of the blood vessels so rapidly that they were either ruptured or closed, localized necrosis of the intestinal wall resulting. The latter view is based on the assumption that the endothelial lining of blood vessels is a part of the reticulo-endothelial system—a part of the defense mechanism.

REPORT OF CASES

CASE 1.—The patient was a large, well developed man. Although there was edema of the entire body, one could see that there had been loss of tissue. When I (C. C. Dennie) saw the patient he was unconscious. He had a well developed arsphenamine dermatitis. The abdomen was greatly distended. While the patient was being examined he expelled a large amount of brownish thin foul-smelling liquid. The pulse was rapid and irregular; breathing was shallow. It was evident that the patient was suffering from paralytic ileus with peritonitis and was in a state of complete coma.

The conditions under which I saw him were primitive. His residence was located 20 miles (12.42 kilometers) from a railroad and there were no hospital facilities in the town. Physiologic solution of sodium chloride was prepared as nearly correctly as possible and a crude intravenous outfit was arranged. This was used successfully, but the patient died four hours later. Autopsy was not performed.

CASE 2.—*History and Symptoms.*—A woman aged 50 six weeks previously had complained of a painful swelling over the right tibia, which had been diagnosed as a syphilitic subperiosteal hemorrhage. The Wassermann reaction was positive. The patient was given 0.45 Gm. of neoarsphenamine and three injections of 0.6 Gm. at weekly intervals. No reactions were noted until three days after the fourth injection, when the patient complained of loss of appetite, persistent vomiting and generalized aching. Swelling of the face, hands and lower portion of the legs was noted at the time. The edema of the eyelids was so marked that it prevented their movement. The condition was diagnosed as arsenical dermatitis, and the patient was hospitalized on March 14, 1935.

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14. Black, Noble: An Unusual Reaction Following Arsenical Treatment of Syphilis, Canad. M. A. J. **22**:673, 1930.

15. Phelps, J. R., and Washburn, W. A.: Urol. & Cutan. Rev. **34**:458, 1930.

Examination and Course.—The entire surface of the body was edematous, the edema being more marked on the face and extremities. The skin on the flexor surfaces of the elbows, knees and groins showed marked weeping with numerous fissures. Examination of the eyes was unsatisfactory because of edema. There was also edema of the lips and tongue. There was considerable cervical adenopathy. The lungs were normal. The heart rate was 140 per minute; the first sound was practically inaudible; the second was loud and accompanied by a diastolic murmur. The abdomen was greatly distended, and there was generalized tenderness. The edge of the liver could be palpated but was less tender than the rest of the abdomen. The entire abdomen felt as if it were filled with dough. The extremities showed marked edema with cracking and weeping in the folds of the skin; patellar reflexes were absent, and marked tenderness was noted over the right tibia. The urine contained from 20 to 40 pus cells per high power field, a few finely granular casts and a trace of albumin. The red blood cell count was 4,330,000; the white blood cell count, 11,400, and the hemoglobin content, 78 per cent. The results of the differential count were as follows: transitionals, 1 per cent; polymorphonuclears, 85 per cent, and eosinophils, 3 per cent. The temperature was 103 F. on admission. The blood pressure was 140 systolic and 80 diastolic.

On March 16 the temperature was 101 F. and the pulse rate 110; there were marked exfoliation of the epidermis, nausea and vomiting. The blood pressure was 140 systolic and 80 diastolic. There was less edema of the skin.

Examination of the blood on March 18 gave practically the same results as on admission, except for eosinophilia, the percentage of eosinophils being 14, and the presence of 9 per cent of metamyelocytes. Distention and tenderness of the abdomen were more marked.

On March 20 the distention of the abdomen was still present. Vomiting of fecal matter and loss of control of the bladder and bowels occurred.

On March 23 the temperature was 106 F. and the pulse rate 130. Vomiting of fecal matter occurred. The patient was comatose. Marked pulmonary edema developed just before death.

Treatment.—The medication had been as follows: digitalis as a cardiac support; 30 grains (1.95 Gm.) of sodium thiosulfate and of calcium gluconate three times a day, 15 grains (0.975 Gm.) of sodium thiosulfate given intramuscularly daily, and pentobarbital sodium for restlessness.

After a diagnosis of paralytic ileus was made 10 Gm. of sodium chloride and 50 Gm. of dextrose were given intravenously daily. Two blood transfusions were given on successive days, 500 cc. of blood being given at each transfusion.

Autopsy.—The postmortem examination was incomplete, only section of different organs being allowed. The peritoneal cavity contained about 2,000 cc. of fecal and watery fluid. The peritoneal surfaces were covered by a profuse fibrinous exudate.

The lungs were crepitant but showed some congestion.

The heart was normal in size but flabby.

The liver weighed approximately 1,500 Gm.; it was soft and flabby, had a greasy feel and showed fairly distinct lobulation.

The spleen was slightly enlarged and soft.

The kidneys were normal in size and showed scarring and pitting on the surface.

The stomach was distended.

There were three perforations in the ascending colon. There were marked inflammation and ulceration of the large intestine. This condition was not noted in the small intestine.

Examination of the stomach and of most of the small bowel was not permitted at the autopsy.

Histologic Examination: The heart muscle showed considerable degeneration with abundant fragmentation and segmentation in some places but no other changes worthy of special note.

The liver showed considerable fatty change, particularly around the peripheral zone.

The kidneys showed rather extensive cloudy swelling. Most of the glomeruli were relatively avascular, though a few of them were slightly congested. Some thickening of the basement membrane was seen. The picture in the kidneys suggested an early chonic nephrosclerosis. A few hyalinized glomeruli could be seen scattered here and there. A few hyaline casts were also seen.

The lungs were quite congested.

A section through the large intestine showed considerable thickening of the wall, some loose adhesions on the surface and many fibroblasts and young connective tissue cells scattered throughout. The submucosa was thickened. The mucosa was more or less disintegrated and broken down and in some places showed extensive ulceration and necrosis which extended even through the wall, apparently representing the edge of a perforation.

Another section through the bowel showed disintegration of the mucosa and rather extensive diffuse infiltration of mononuclear and polymorphonuclear leukocytes throughout. Clumps of bacteria could be seen in a few places. A thick fibrinous exudate was seen over the surface of the serosa in some places.

In commenting on the pathologic changes, H. R. Wahl made the following statements: "Death was due to the toxemia resulting from the perforation and rather extensive ulcerative colitis. It is possible that this ulcerative colitis may have been a part of an arsenical enteritis and colitis associated with extensive exfoliative dermatitis. This complication of arsenical poisoning is, of course, unusual. The exfoliative dermatitis was fairly typical of the arsenical type. As arsenic had been used, it probably was the cause of the cutaneous lesion. The extensive involvement of the skin may account for the severe gastro-enteritis associated with ulceration, perforation and peritonitis.

"The anatomic diagnosis is acute exfoliative dermatitis, acute ulcerative colitis (enteritis?) with multiple perforations of the ascending colon, acute generalized fibrinopurulent peritonitis, hydroperitoneum, chronic nephrosclerosis with acute toxic nephrosis superimposed, fatty change in the liver and congestion of the lungs."

COMMENT

There is no doubt that in case 2 the patient died of peritonitis due to the perforation of the intestinal wall.

It is well known that arsenic taken in toxic doses by mouth produces rice water stools. One must admit that some of the toxic action in this instance must have been due to the corrosive action of the arsenic directly on the intestinal mucosa. Is it not possible that at times some of the absorbed arsenic may be deposited in that mucosa by the blood stream? One of the common complications in intravenous arsenical therapy is the occurrence of severe diarrhea, which is probably due to the toxic action of the blood-borne arsenic.

It is possible that this reaction is entirely independent of any action on the small blood vessels of the intestine. We believe that the action of arsenic, both on the wall of the blood vessel and on the intestines, was responsible for the necrosis and consequent perforation of the large intestine in case 2.

Both patients had an adynamic paralytic ileus. Whether the ileus preceded the perforation of the intestine is a debatable question.

Patients with paralytic ileus have been known to recover. I (C. C. D.) have often wondered why not more patients exhibit this complication, since I have seen a few who had the preliminary signs. I believe that the paralytic ileus preceded the perforation and was due to the toxic action of the arsenic on the vegetative nervous system. The condition is comparable to that which takes place in cases of severe burns simultaneously or shortly after the ileus is produced. The specific action of the arsenic on the walls of the blood vessels, the endothelial lining and the perivascular lymph spaces no doubt produced the hemorrhages, thrombosis and rupture of the vessels. It is also conceivable that arsenic borne through the lymph and blood streams produced a specific corrosive action on the mucous membrane. The latter accidents happening in a paralyzed intestine could easily cause a perforation.

CONCLUSION

Perforation of the intestine is one of the complications of arsphenamine dermatitis.

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ABSTRACT OF DISCUSSION ON SYMPOSIUM

Dr. Edward R. Maloney, New York: In the past months my co-workers and I treated 92 patients with mapharsen and obtained results similar to those reported by Dr. Weider and his associates. We have had cases of jaundice, and there have been no serious reactions. In some cases there has been nausea, occasionally accompanied by vomiting. We found that these disturbances occurred after several doses of mapharsen had been given. We now limit the treatment to series of eight doses and follow that with administration of bismuth. Several patients have complained of pain in the arm after injection and we found that this was increased, as Dr. Wieder and his associates said, when the injection was given slowly. We tried to use mapharsen intramuscularly in treating children, but we had to give it up because they had too much pain. We do not have much difficulty with extravasation, as any irritation produced soon passes away.

We feel that mapharsen is a useful drug in the treatment of syphilis, and we believe that it is of about the same value as neoarsphenamine but not as good as old arsphenamine.

Dr. Carroll S. Wright, Philadelphia: I have had limited clinical experience with mapharsen, but I have observed the absence of reaction which has been men-

tioned. I am impressed by the discrepancy in the results of laboratory tests with mapharsen as reported from different sources. In a recent paper Gruhzit stated that the maximum intramuscular dose of mapharsen tolerated by rats was 22 mg., but studies made in a laboratory in Philadelphia have shown that the intravenous dose of mapharsen tolerated by rats is 18 mg. per kilogram of body weight. This compares with the maximum tolerated dose of neoarsphenamine, which is 400 mg. per kilogram of body weight. Gruhzit reported that for rabbits and guinea-pigs the maximum dose which could safely be injected intravenously is 14 mg., whereas the laboratory in Philadelphia reported that it is 11 mg. This compares with a maximum tolerated dose for neoarsphenamine of 200 mg. per kilogram, the dose given to rabbits. Of course, cognizance is taken of this difference in tolerated doses by the manufacturers of mapharsen, and they recommend that it be given in doses not exceeding 60 mg., whereas doses of neoarsphenamine range from 300 to 600 mg. per kilogram. It must be determined whether inadequate treatment of syphilis will result from the small amount of mapharsen used.

One must realize, furthermore, that mapharsen is an arsenoxide, which is by no means a new product. It was known in the chemical literature twenty-five years ago. It was studied by Paul Ehrlich, who abandoned its use because of the high toxicity. It seems to me that some further study of the dose tolerated by syphilitic rabbits should be undertaken because of the discrepancy in the reports of different laboratories to date. Tests on syphilitic rabbits have always been considered the most important source of information available.

These statements are not at all intended as a criticism of the value of mapharsen in the treatment of acquired syphilis in man, but on the basis of work that has been done I can see no points of superiority of mapharsen over neoarsphenamine, and I am inclined to believe that it is actually less efficacious as a therapeutic agent. Reports such as that presented by Dr. Wieder and his co-workers are helpful in aiding one to arrive at a final conclusion as to the value of this agent as a therapeutic weapon against syphilis.

Dr. V. Pardo-Castello, Havana, Cuba: In reference to Dr. Cole's paper on interstitial keratitis, I wish to say that I do not know of a more discouraging condition than that. It is true that if proper treatment is given early acute interstitial keratitis clears up, but unfortunately most patients are seen when they have been suffering for many months; some are not treated until they are almost entirely blind, and nothing can be done for them. In cases in which the condition was resistant I have used fever therapy with some success and without much risk. I hesitated to give malaria or intravenous vaccine therapy and therefore decided to use a 2 per cent suspension of sulfur in oil, a preparation which has been employed before. The only objection to this is the local pain, but I found that when the proper technic was used and the child was put to bed immediately after the injection the pain was less severe. The rise in temperature as a rule is satisfactory. About six hours after the injection the temperature rises to from 103 to 104 F., and that temperature is maintained for about six hours. About from ten to sixteen injections are given, and after a few months another course may be administered. Arsphenamine therapy is employed after the fever treatment.

Regarding mapharsen, I have had slight experience with this drug and cannot speak much of the advantages and disadvantages of its use. It seems to me, however, that a new drug which offers no definite advantage in treatment has no place in the therapeutics of syphilis. If the new drug makes it possible to treat syphilis more accurately and with better results than has been possible previously, that is well, but if it does not I shall not consider the drug as a substitute for the arsphenamines.

Dr. Joseph V. Klauder, Philadelphia: The curious features of interstitial keratitis constitute, I believe, the most interesting problems in syphilology and have not received the attention they deserve. Why is interstitial keratitis seen almost exclusively in patients with congenital syphilis, and why is the second eye involved even during treatment? It is interesting to note that Jonathan Hutchinson considered that the two eyes act as one organ, as he stated in explanation of his observations, that symmetrical diseases are always manifested first on one side and that simultaneous bilateral involvement is rare. Others believe that the incubation period is different for each eye. Still others regard interstitial keratitis as a sensitization phenomenon. It is to be recalled that according to the experiments of Wessely the cornea of a rabbit can be sensitized to horse serum, the resulting keratitis pursuing a course somewhat comparable to that of interstitial keratitis in cases of congenital syphilis.

Regarding therapeusis, there is apparently a considerable difference in individual response to antisyphilitic treatment. In some patients the condition runs an acute and severe course despite all methods of treatment. In these patients the second eye is invariably involved. In others the keratitis responds to treatment and the results are good. In a third group the interstitial keratitis apparently runs a mild course without treatment. In studies made at the clinic at the Wills Hospital in Philadelphia, it was noted that in patients who had received no treatment the keratitis involuted after having pursued a mild course.

A different approach of the treatment of interstitial keratitis is desirable. My co-workers and I employed the thermophore. In experiments with rabbits we demonstrated that when the thermophore was applied to the anterior surfaces of the corneas the posterior surfaces could be heated to 104 F., which is about the lethal temperature for Spirochaeta pallida. This study was carried out by means of the thermocouple. In children with unilateral interstitial keratitis we treated the uninvolved eye with the thermophore in the hope of preventing its involvement. Such involvement occurred, however, despite a number of previous applications of the thermophore. This experience does not show the presence of Spirochaeta pallida in the cornea, the site of interstitial keratitis, and is in line with our failure to demonstrate the organism in pieces of cornea removed from patients with interstitial keratitis.

Dr. Jacob H. Swartz, Boston: In reference to the paper by Dr. Weider and his co-workers, I wish to mention one case of severe nitritoid reaction occurring after the fourth injection of 0.02 Gm. of mapharsen in 40 cc. of water. A temperature of 103 F., lasting for three days, severe backache, nausea and vomiting developed, and a great deal of treatment was necessary to get the patient out of shock. He is doing well now on bismuth therapy.

Dr. Samuel E. Sweitzer, Minneapolis: In respect to the paper by Dr. O'Leary and his co-workers I wish to say that the subject of neurosyphilis interests me greatly. Quite a number of patients with that condition are seen; in many instances the involvement is asymptomatic. I did not quite understand whether the authors used routine treatment in all their cases of early or late syphilis and obtained the results shown in the charts. In Minneapolis some patients are treated in the neurologic department and some are treated in the dermatologic department. The neurologic department has been reluctant to use malaria therapy and has used routine treatment in many instances. Sometimes patients treated in that department are seen by dermatologists, and my co-workers and I have felt that the routine treatment was not bringing results. Because of that in cases of latent syphilis we examine the spinal fluid, and if it is abnormal and the patient is in good physical condition we give malaria therapy at once and follow that with the

routine treatment. I think that somewhat better results are obtained in this way than if the patient first received routine therapy for a number of months or years and then, failing to improve, was given malaria therapy. I find that in private practice examinations of the spinal fluid are difficult to obtain, but in the clinic patients do not object to them so much.

I think that the proper course might perhaps be administration of malaria therapy followed by routine treatment.

DR. ELMORE B. TAUBER, Cincinnati: I have had little clinical experience with mapharsen, but I think that the criticism made by the speakers should not be taken too critically. Many sequelae from other arsenicals, such as exfoliative dermatitis, do occur, and in treating patients who cannot tolerate the other arsphenamines my co-workers and I have changed to mapharsen. We have not observed a recurrence of these evidences of susceptibility to arsenic.

DR. E. J. TROW, Toronto, Canada: I think treatment is important. I came here rather satisfied with the type of treatment my co-workers and I had been using for a number of years—the intermittent form. It was not until Dr. Stokes stated that this is not so good as the continuous form that I became dissatisfied, and I think that when I go home I must see if improvements can be made. We began using the intermittent type of therapy in 1929 and have administered it to about 336 patients with early syphilis since then. Of 193 patients whom we considered adequately treated for a year or more, 99, or 51 per cent, were cured. There were no neurorecurrences. There was 1 mucocutaneous recurrence. There were no fatalities, although several reactions, including nitritoid crises and dermatitis, did occur.

It seems to us that the method of continuous treatment is discouraging to the patient. He sees no end to it, and it may be that rest periods of three, four or even five weeks, such as we give, are pleasing to him. He feels that he is getting on, that he has finished one course and that although he must take another he is, nevertheless, progressing.

DR. HAROLD N. COLE, Cleveland: In our paper my co-workers and I emphasized that prophylaxis is the best treatment of interstitial keratitis. If the patients are seen early, if they are treated within the first two months and if adequate amounts of arsphenamine are given, the condition will respond to therapy. The great difficulty is that most of these patients are treated by ophthalmologists and do not receive arsphenamine, which is the drug that gives results. In cases of long standing foreign protein therapy may be necessary. We do not hesitate to give these patients malaria therapy, and we have seen some striking results. After the first one or two chills the patients are able to see a great deal better than before.

DR. PAUL A. O'LEARY, Rochester, Minn.: The answer to the question raised by Dr. Sweitzer is embodied in the papaer. I have been informed that a legal authority for the State Medical Society of New York has expressed the opinion that an examination of the spinal fluid is now essential in the adequate treatment of syphilis. Accordingly, a physician who treats a patient for syphilis and does not examine the spinal fluid may be prosecuted for malpractice unless he can show that such an examination was contraindicated.

DR. LESTER M. WIEDER, Milwaukee: In regard to the gastro-intestinal reactions mentioned by Dr. Maloney, I wish to say that such reactions have occurred in our experience, but they can usually be eliminated by adjusting the dosage to the tolerance of the patient.

We are aware that a discrepancy exists in the results of laboratory tests relative to the therapeutic efficiency and toxicity of mapharsen in experimental animals

as published by different workers. We are not in a position to comment on this phase of the subject, being concerned only with the clinical aspects of the drug, and we can cite only our own observations.

In reply to Dr. Pardo-Castello's comments, I regret that I could not describe in the short time allowed a number of things that favor the use of mapharsen. The serious reactions are exceedingly infrequent, and as was illustrated in the case of interstitial keratitis to which I referred, response to mapharsen after the failure of other therapy and other similar clinical results shows that the preparation is a valuable addition to the existing antisyphilitic drugs.

My co-workers and I wish to be conservative in our appraisal of this preparation, but we feel that it is a drug of value and that it has a place in the treatment of syphilis.

TREATMENT OF SCABIES WITH THE SO-CALLED DANISH METHOD

ARTHUR M. GREENWOOD, M.D.
AND
MARGARET REILLY, R.N.
BOSTON

In treatment of a disease such as scabies, which is so prevalent and contagious and the cure of which depends on the meticulous observation of the rules of treatment, it is important that the therapeutic measures be simple, short and effective.

The ointment used in the so-called Danish method originated in Copenhagen in 1911. It was reported on by Dr. Svend Lomholt in 1920;[1] its use was introduced at the Massachusetts General Hospital in 1923,[2] and it has been used at that hospital ever since. An important consideration from the clinician's point of view is that the ointment is applied once and left on for twenty-four hours, no further application being necessary. This report is a survey of the results of the use of that preparation during ten of the years since its adoption as the exclusive treatment of scabies in the clinic of the Massachusetts General Hospital.

In these ten years there have been treated 2,582 patients whose clinical records are available and 1,940 contacts, a total of 4,522 persons. As no accurate record of these contacts is kept, only their number being known, they have not been considered in the computation of the percentage.

Of the 2,582 patients, 63 per cent, or 1,639, made only one visit to the clinic and are assumed to have been cured. We feel that this is a reasonably justifiable assumption, for as these patients were all reported on and followed by a visiting or school nurse they would have been sent back to the hospital if that had been necessary.

Seventy-eight per cent of the patients were between 1 and 30, and 33 per cent were between 10 and 20, years of age. As far as seasonal incidence is concerned, the smallest number of cases were observed during the summer. We have found that a single treatment was successful in 93.85 per cent of the cases. In 5.6 per cent, 144 cases, a dermatitis followed the one application of the ointment.

Read at the Fifty-Ninth Annual Meeting of the American Dermatological Association, Inc., Swampscott, Mass., June 4-6, 1936.

1. Lomholt, S.: Lancet **2**:1251 (Dec. 18) 1920.

2. Greenwood, Arthur M.: The Danish Treatment of Scabies, J. A. M. A. **82**: 466 (Feb. 9) 1924.

ROUTINE FOR TWENTY-FOUR HOUR TREATMENT

Printed directions are given; they are as follows:

This disease is very contagious.

All the members of the family who itch or who have slept with a patient who itches must be treated at the same time if the family wish to secure a permanent cure and prevent reinfections. Treat as follows:

All take a good hot bath, using soap and scrubbing the body all over carefully with a small brush or coarse wash cloth.

After the bath apply to the body from chin to toes, back and front, the ointment given to you by the doctor. Hard rubbing is not necessary. Do not rub ointment on face or scalp.

Leave this treatment on for 24 hours. Then take a cornstarch bath and put on freshly boiled and pressed underclothing. Put freshly boiled and pressed linen on your bed.

Take all your soiled clothes, including night clothes and underclothing, as well as sheets, pillow cases and towels, put them into a boiler or large pan on the stove and cook 20 minutes. Press twice with a hot iron everything which comes in contact with the skin and cannot be boiled, especially gloves and stockings.

Return to the hospital or consult your doctor or nurse in 2 weeks and they will tell you if you are cured.

Do not use ointment after the 24 hours without consulting your doctor.

COMMENT

It is important that these instructions be given to a dependable adult member of the family, and if there seems to be a lack of understanding because of intellectual handicap or difficulty in language the treatment is withheld until the visiting or school nurse can go to the home and give a practical demonstration. If the patients live near the hospital, frequently whole families are treated in the emergency ward when treatment at home seems impossible.

The visiting or school nurse is notified and visits the family after the twenty-four hour treatment, and children are examined before they are permitted to return to school. After their return to school they are reexamined each week by the nurse or by the school physician. Children are regularly allowed to return to school after twenty-four hours if there is no secondary infection.

To prepare school and visiting nurses for a complete understanding of the problem of scabies and of the technic of the twenty-four hour method, lectures and demonstrations are given, and we have had extraordinary cooperation from the nurses and from the patients in carrying out the method. The patients appreciate the advantages of the method in that it does not keep the father from work or the children from school; the nurses appreciate it because they know that a three or five day treatment is entirely unpractical in many families. The amount of water for bathing and the changes of clothing are important factors

in those methods, and the supervision they require is much too time consuming for the nurse.

In most cases the entire family is treated—certainly every one in the group who could by any possible chance have been exposed receives treatment. As a routine we advise that starch baths be taken and calamine lotion applied after the treatment. This not only tends to prevent a dermatitis but lessens the temptation for the patient to reapply the ointment if the itching has not entirely ceased. It is not necessary, in our experience, to modify the treatment for babies, except that a less vigorous scrubbing is required before the ointment is applied. We have never seen a case of sulfur dermatitis in an infant treated by this method.

Patients should be warned not to wash their hands during the twenty-four hours following the application of the ointment, and to prevent them from disregarding this rule, they should be instructed to wear cotton gloves; children may wear stockings on the hands when gloves are not available. This is an important point in technic, and its omission is a frequent cause of failure.

Before 1923 we had always used the three day method and employed sulfur and betanaphthol, and recently we have tried in a small number of cases, and with almost complete lack of success, a two hour treatment with a commercial preparation in liquid form. On the basis of our experience we feel quite definitely that the twenty-four hour method with the ointment previously described[2] is the most successful, the least likely to irritate the skin and the most economic of any of the methods with which we are familiar. We believe that method can safely be recommended, especially for use in clinics, but we also feel definitely that the strictest attention to detail as regards instructions to patients, technic, treatment of contacts and follow-up are just as essential as the use of any specific ointment. It is probable that this method of treatment is successful largely because it makes comparatively easy the carrying out of such details.

The formula and the method of compounding the ointment have been published in Dr. Lomholt's [1] report; later a more detailed description of the way it is made at the Massachusetts General Hospital has been given.[2] If the ointment is not properly made it can cause a severe alkali burn, and probably it should not be made in small quantities by any pharmacist as the occasion for its use arises. It is possible and permissible to make it in large quantities and to keep it for months. When this is done there occurs a small amount of oxidization at the surface; this, however, is not sufficient to change the therapeutic efficacy of the ointment as a whole.

SUMMARY

This is a report on 4,522 cases of scabies in which the so-called Danish method of treatment was used. In 93.85 per cent of the cases cure resulted from a single application of the ointment. In 5.6 per cent a dermatitis followed its use.

Directions are given for the use of the ointment, and the public health aspects of this treatment are discussed.

ABSTRACT OF DISCUSSION

DR. E. L. OLIVER, Boston: I congratulate Dr. Greenwood on his results. I have observed many of his cases in the last fourteen years, during which time he has been using this ointment, and the results have been extremely good. I think his percentage of failures was about 7, but I believe this figure is much higher than the true one, for when I interviewed the patients, treatment of whom was classed as failure, I found that a large majority of them had not followed the technic correctly. Either they did not have enough of the ointment to apply properly, or they had not followed the directions. I think that if the directions are carefully carried out the percentage of failures would not be above 2. I feel that this is the best treatment for scabies.

DR. SAMUEL E. SWEITZER, Minneapolis: The paper of Dr. Greenwood interested me. My co-workers and I have apparently about the same incidence of scabies in our clinic that he reports. We have observed 1,200 cases in about two years.

My approach to scabies is from the diagnostic angle. It is a common disease, but recently Dr. Stokes called the attention of the medical profession to the difficulty of diagnosing scabies. He stated that in private practice he has observed many cases which had previously been studied by dermatologists and in which the diagnosis had been missed. I remember that during a visit I made to the St. Louis hospital in Paris, France, I saw some gentlemen with long whiskers debate for some time as to whether a certain patient had scabies or not, but I do not think that is often the case.

I think the most important part of treatment is the vigorous first bath and the opening of the lesions that still carry the parasite. One has to contend with the ignorance of the patients who will not follow directions for thorough baths. I think that this is the general experience.

The treatment which the authors describe has not been satisfactory when used by my colleagues and me for we could not get the ointment made right. Where pharmacists have more experience in making it the treatment is apparently successful. The treatment with other ointments containing sulfur, such as that prepared by the formula of Wilkinson or of Stokes, produces a tremendous amount of dermatitis, which necessitates treatment for some weeks after the scabies is cured. Many patients come to the clinic after using sulfur ointment, and my co-workers and I are able to spot those patients almost at once. In our clinic recently we have used an ointment with Pyrethrum in several hundred cases. This is a good remedy to use in private practice, for it has a pleasant odor and is efficient. I know that dermatologists who place much importance on allergy will shudder at the mention of Pyrethrum, but many patients are more sensitive to eggs than they are to that substance, and I have observed few cases of dermatitis following its use. I think it is efficient except for the pustular form of scabies. In treating that form I use the ointment recommended by Wilkinson.

Dr. Jacob H. Swartz, Boston: I wish to emphasize Dr. Greenwood's statement regarding the necessity for a proper preparation. I have observed multiple keloid scars which appeared on the chest and neck of a young lady as a result of improperly prepared ointment used in the so-called Danish method.

Dr. Arthur M. Greenwood, Boston: I think Dr. Sweitzer will agree that while Pyrethrum is agreeable and pleasant to use it is not at all adaptable for use in a large clinic.

ARSPHENAMINE-RESISTANT SYPHILIS

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CLEVELAND

The rapid disappearance of the spirochetes (Spirochaeta pallida) from the chancre and the relatively prompt healing of the cutaneous and mucosal manifestations of early syphilis following the administration of arsphenamine are some of the spectacular achievements of chemotherapy. Furthermore, the observations of the Cooperative Clinical Group [1] show that the adequate treatment of acute syphilis by the continuous and judicious use of modern antisyphilitic remedies produces a clinical and serologic cure in a large proportion of cases. With this advancement in the treatment of syphilis differences of opinion have arisen regarding the influence of modern antisyphilitic drugs on the course of the disease, and the medical literature is replete with articles in which the various phases of this complex problem are discussed. Some observers have argued that since the introduction of arsphenamine there has been an increase in the incidence of late visceral manifestations of syphilis and that in cases in which such complications occur the usual period in which no symptoms are present has been shortened. Some writers have also felt that early syphilis is becoming more resistant to treatment and that instances of Wassermann fastness have become more frequent in recent years. The accumulated evidence indicates that the increase in the incidence of late visceral manifestations of syphilis is more an apparent than an actual increase and that the interval between the date of infection and the onset of the late manifestations has been shortened since the introduction of arsphenamine. Most authorities attribute this shortening of the period in which no symptoms are present to inadequate and injudicious use of arsphenamine rather than to a change in the biologic properties of the spirochetes.

Since the Great War an increasing number of cases of arsphenamine-resistant early syphilis have been reported in the European literature;

From the Cleveland Clinic.

Read before the Section on Dermatology and Syphilology at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 15, 1936.

1. Stokes, J. H.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Parran, T., Jr.; Vonderlehr, R. A, and Usilton, L. J.: Standard Treatment Procedure in Early Syphilis, J. A. M. A. **102**:1267-1272 (April 21) 1934.

however, during the past decade, comparatively few reports of cases of that kind of syphilis have appeared in the American literature. It is questionable whether a lack of interest in this subject or the infrequent occurrence of resistant syphilis is responsible for the paucity of reports by American observers. It is interesting to note that in most of the reported cases the resistance has been to one of the arsphenamines; however, in rare cases the infection has been resistant to arsphenamine, to bismuth and to mercury. This apparent increase in the number of cases in which early syphilis fails to respond promptly to the most therapeutically active antisyphilitic remedy has awakened considerable interest and has stimulated European observers to further discussion of the old debatable question of the possible development of an arsphenamine-resistant strain of S. pallida.

In 1930 Moore and Robinson [2] reviewed the important German contributions dealing with arsphenamine-resistant syphilis and made a study of the records of 1,116 patients with early syphilis treated in the syphilis division of the medical clinic of Johns Hopkins Hospital from 1914 to 1927. In this series there was no increase in the number of relapses of a secondary type and no significant difference in serologic results in the more recent period as compared with those in earlier years. According to Moore and Robinson, since the establishment of the clinic about a dozen cases of true arsphenamine-resistant syphilis had been observed, and the incidence of cases of that kind of syphilis had not increased in recent years. They concluded, therefore, that there had been no increase in the incidence of arsphenamine-resistant syphilis in their locality.

More recently Miller [3] reported a case of primary syphilis which was resistant to arsphenamine but which later responded to the intramuscular injection of sulfarsphenamine and a bismuth preparation. The arsphenamine which was used in this case was shown to have a high trypanocidal activity. Miller also cited several communications on arsphenamine-resistant syphilis which have appeared in the French literature.

It is difficult to explain this difference in the efficacy of antisyphilitic therapy reported on the two continents. Moore and Robinson [2] have suggested that possibly the altered nutrition of Europeans due to deprivations during the Great War may have been a factor in the production of arsphenamine-resistant syphilis in Germany.

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2. Moore, J. E., and Robinson, H. M.: Question of Arsphenamine-Resistant Syphilis, Arch. Dermat. & Syph. **21**:32-39 (Jan.) 1930.

3. Miller, Thomas H.: Problem of Arsphenamine-Resistant Syphilis: Report of a Case, J. A. M. A. **97**:11-14 (July 4) 1931.

Early syphilis may be classified as resistant when intensive treatment fails to remove promptly and permanently all mucocutaneous manifestations of the disease. The most positive proof of resistance is the persistence of spirochetes in the lesions in spite of intensive treatment.

Arsphenamine resistance is a characteristic of early syphilis and must not be confused with the slow response of the lesions of late syphilis to antisyphilitic treatment. Moore [4] stated that the mucosal and cutaneous manifestations in arsenoresistant syphilis may react to the drug in one of three ways:

1. The lesions may enlarge, become more numerous and continue to contain motile spirochetes. This type of response is rare.

2. The initial injections may produce a partial involution of the lesions, continued administration of the drug, however, failing to prevent a reappearance of the eruption.

3. The lesions may react favorably to arsphenamine, relapses occurring when the heavy metals are given.

Wassermann fastness in early syphilis is usually an indication of visceral involvement and should not be interpreted as a manifestation of drug resistance until the possibility of asymptomatic neurosyphilis or involvement of the cardiovascular system has been eliminated.

Moore and Kemp [5] have observed that recurrence of a positive reaction occurs more frequently in cases of early syphilis in which there are premature reversals of the Wassermann reaction than in cases in which there is a delayed serologic response to treatment, and they have suggested that in these cases the body defense reaction fails to respond in the usual manner to the presence of the spirochetes.

Malignant syphilis, characterized by large ulcerations, by loss of weight, by fever, by drug resistance, in some cases by a negative serologic reaction and frequently by a fatal termination, must be distinguished from the arsphenamine-resistant syphilis which apparently has become more prevalent in Europe within the past decade. Malignant syphilis has been discussed by Wile, Wieder and Warthin,[6] Gadrat,[7] Milian,[8] Sylvestre,[9] Lacapère and Decrop [10] and others.

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4. Moore, Joseph Earle: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, pp. 38, 204 and 249.

5. Moore, J. E., and Kemp, J. E.: Treatment of Early Syphilis: Wassermann Reaction in Treated Early Syphilis, Bull. Johns Hopkins Hosp. **39**:36-55 (July) 1926.

6. Wile, U. J.; Wieder, L., and Warthin, A. S.: Malignant Syphilis with New Explanation of Pathology of Cutaneous Lesions, Am. J. Syph. & Neurol. **14**: 1-34 (Jan.) 1930.

7. Gadrat, J.: Syphilis maligne totalement anergique et mortelle, Ann. de dermat. et syph. **5**:990-1008 (Nov.) 1934.

(Footnotes continued on next page)

The problem of arsphenamine-resistant syphilis is of practical and theoretical importance. Arsphenamine is the most potent of modern antisyphilitic remedies; therefore, the failure of the acute manifestations of the disease to respond to this drug greatly increases the possibility of a further spread of the infection. A few persons with resistant early syphilis, as manifested by frequent recurrences of mucocutaneous eruptions of the moist type, are grave menaces to the public health of any community. Theoretically, the problem of drug-resistant syphilis is of interest because it embraces some of the unsolved questions of chemotherapy. The subject is complex, and its solution is dependent on more exact information than is now available regarding the mode of action of antisyphilitic remedies. In recent years investigators have attributed more importance to the relationship between the activity of the reticuloendothelial system and the chemotherapeutic action of arsphenamine.[11] There is some reason for believing that the cells of this system play a dual rôle, namely, form antibodies and temporarily store chemotherapeutic substances. Another phase of the subject which is of interest is the question of the possible ability of the virus to acquire a tolerance to arsphenamine.

Obviously, the variation in the results which are obtained in cases of adequately and properly treated early syphilis depends on (1) the potency of remedies used, (2) the peculiarities of the virus or host or (3) a combination of these factors.

I have no satisfactory explanation for the less favorable response to arsphenamine therapy in certain cases of early syphilis. It has been suggested that procedures decreasing the toxicity of the drug have brought about alterations which diminish its therapeutic efficiency. That this is not probable is confirmed by the observations that a particular arsphenamine known to possess high trypanocidal properties has proved to be effective in several cases and inefficient in only an occasional case. Most European authorities do not attribute the apparent increase

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8. Milian, G.: Syphilis maligne précoce, Rev. franç. de dermat. et de vénéréol. **6**:336-348 (June) 1930; Syphilis maligne précoce: Manifestations ulcéreuses ultérieures, ibid. **6**:266-268 (May) 1930.

9. Sylvestre, P.: Case of Early Malignant Syphilis, Rev. méd. de la Suisse Rom. **43**:172-177 (March) 1923.

10. Lacapère and Decrop: Le syndrome malin dans la syphilis, Paris méd. **35**:203-208, 1920.

11. The Reticulo-Endothelial System and Chemotherapy, editorial, J. Chemotherapy **8**:120-124 (Jan.) 1932. Kolmer, J. A., and Schamberg, J. F.: The Influence of Reticuloendothelial "Blockade" and Splenectomy upon Experimental Trypanosomiasis and Syphilis and the Chemotherapeutic Properties of Arsphenamine and Neoarsphenamine, Am. J. Syph. & Neurol. **17**:176-187 (April) 1933.

in the incidence of drug-resistant syphilis to a decrease in the chemotherapeutic efficacy of arsphenamine.

For a number of years there has been considerable discussion regarding the production of an arsphenamine-resistant strain of S. pallida. Soon after the introduction of arsphenamine it was discovered that parasites, especially trypanosomes, are able to acquire a resistance to the drug. This led to the experimental production of arsphenamine-resistant strains of trypanosomes in vitro. In most of the investigations the organisms studied have been trypanosomes; however, several workers have shown that various types of spirochetes are capable of acquiring some increased tolerance for arsphenamine, much slighter, however, than that exhibited by the trypanosomes. Yorke [12] has recently reviewed this subject and has shown that the acquired drug resistance of trypanosomes is a stable characteristic which is not lost when the strain is transferred from one host to another. He expressed the opinion that, although there is experimental evidence to show that some degree of drug resistance may be acquired by S. pallida, there is no evidence which indicates that this increased tolerance is an important factor in arsphenamine-resistant syphilis.

Akatsu and Noguchi [13] were among the first observers to show that S. pallida may acquire a resistance to antisyphilitic drugs. They found that by exposing S. pallida to arsphenamine and to mercurial and iodide compounds in vitro, the tolerance of the organism to each drug was increased as much as five and one-half times. The drug resistance gradually disappeared when the organism was cultivated in drug free mediums for several generations. Klauder [14] was the first to investigate this problem by means of experiments in vivo. By the administration of subcurative doses of arsphenamine to rabbits which had been inoculated with S. pallida he was able to increase the resistance of the strain of the infecting organism to the drug as much as 68 per cent.

These observations are important but not conclusive. If the biologic properties of S. pallida can be altered to the extent suggested by the observations of Akatsu and Noguchi and of Klauder it is difficult to understand why arsphenamine-resistant syphilis has not occurred more frequently in man. It is not uncommon for a person with early stages of syphilis to discontinue treatment voluntarily after receiving inade-

12. Yorke, W.: Drug-Resistance, Brit. J. Ven. Dis. **9**:83-109 (April) 1933.

13. Akatsu, S., and Noguchi, H.: The Drug-Fastness of Spirochetes to Arsenic, Mercurial and Iodide Compounds in Vitro, J. Exper. Med. **25**:351-362, 1917.

14. Klauder, J. V.: Experimental Production of an Arsenic Resistant Strain of Spirochaeta Pallida in Rabbits, Arch. Dermat. & Syph. **9**:446-458 (April) 1924.

quate or subcurative treatment which consisted entirely of arsphenamine. However, there has been no apparent increase in the incidence of arsphenamine-resistant syphilis in this country. It is probable that in this country the practice of treating early syphilis with courses of arsphenamine alternating with courses of a heavy metal has been an important factor in preventing the occurrence of a notable change in the spirochetes.

Greenbaum and Rule [15] were unable to corroborate the observations of Klauder.[14] They found that in rabbits repeated exposures of a strain of S. pallida to small doses of neoarsphenamine failed to increase the tolerance of the organism to the drug. In a series of experiments extending over a period of almost three years they passed the same strain of organism which was used by Klauder through nine sets of rabbits by transfer of lymph nodes; however, before the infection was transferred from one set of animals to another set, each animal was given ten injections of a subcurative dose of neoarsphenamine. The lesions in the ninth set of animals disappeared as readily after a curative dose of the drug as did the lesions in the controls.

That arsphenamine resistance is probably not dependent on altered biologic properties of the spirochetes is shown by the observations of Hoffmann and Armuzzi [16] and of Nothaas.[17] These authors observed that rabbits which were inoculated with spirochetes obtained from patients with arsphenamine-resistant syphilis responded as favorably to treatment as did rabbits which were infected with other strains of S. pallida. As an explanation for this apparent inconsistency in results Miller [3] has made the pertinent suggestion that the resistance which may be dependent on chemical factors present in the host may not become manifest when the organism is transferred to a host of a different species. Because of the variation in the host, the information which is obtained from experiments with animals cannot be applied to the interpretation of the problems of human syphilis without some reservation. Therefore, experimental evidence must ultimately be correlated with the facts obtained from clinical observations.

Beerman [18] has recently made an exhaustive review of the literature dealing with treatment-resistant syphilis and has reported his own

15. Greenbaum, Sigmund S., and Rule, Anna M.: Resistant Syphilis, with Especial Reference to an Attempt to Produce Experimentally an Arsenic-Resistant Strain of Spirochaeta Pallida, Pennsylvania M. J. **39**:339-343 (Feb.) 1936.

16. Hoffmann and Armuzzi, cited by Moore and Robinson.[2]

17. Nothaas, cited by Moore and Robinson.[2]

18. Beerman, Herman: Problem of Treatment-Resistant Syphilis, with Special Reference to Arsphenamine-Resistant Syphilis: Review of Literature and Experimental Study, Am. J. Syph., Gonor. & Ven. Dis. **20**:296-334 (May) 1936.

experimental observations with a strain of S. pallida which he isolated in a case of arsphenamine-resistant syphilis. He found that the opinions recorded in the literature were slightly in favor of the existence of strains of S. pallida with different biologic characteristics. He also found that for the most part investigators were unable to demonstrate drug resistance in experimental animals when the disease was produced by strains of S. pallida which were isolated from persons with arseno-resistant syphilis. In Beerman's experiments, five of twenty-five rabbits infected with a strain of S. pallida isolated from his patient were not cured by doses of arsphenamine slightly greater than the minimal sterilizing dose established for the Nichols strain of S. pallida. He concluded that these observations suggested that the organism isolated in his case possessed some refractoriness to the arsenicals.

An ideal opportunity for studying the influence of the drug, the organism and the host in the course of a syphilitic infection is presented in instances in which two or more patients are known to be infected with the same strain of spirochete. The observation of a large series of cases in which these conditions obtain should give some indication regarding the existence of an arsphenamine-resistant strain of S. pallida.

A review of the literature reveals that there is a diversity of opinion regarding the question of whether the extensive use of arsphenamine is producing an arsenoresistant strain of S. pallida. Some European observers are convinced that arsphenamine-resistant syphilis is actually becoming more frequent, and they have expressed the belief that the seed, or S. pallida, must be incriminated, while others have voiced the opinion that the resistance depends on some peculiarity of the host. Instances of conjugal syphilis in which arsphenamine resistance occurred in the husband or in the wife or in both have been reported; however, the number of such observations is too small to be of value. Since in instances of conjugal syphilis arsenoresistance has been observed in both matrimonial partners as well as in only one of them, it is doubtful whether an alteration in the biologic properties of S. pallida plays an important rôle in the production of arsphenamine-resistant syphilis.

Kloeppel [19] observed the case of a married couple in which each person had an arsphenamine-resistant chancre associated with a negative serologic reaction. In each person the lesion healed promptly after administration of mercury and bismuth. Apparently Kloeppel assumed that the arsenical which he used in these cases was trypanocidally active,

19. Kloeppel, F. W.: Salvarsanresistenter Spirochätenstamm bei einem Ehepaar, München. med. Wchnschr. **73**:1936-1937 (Nov.) 1926.

for he concluded that strains of S. pallida exist which have biologic variants.

Nicolas, Massia and Lacassagne [20] have been impressed by the increase in the number of cases of arsphenamine-resistant early syphilis which they have observed since 1925. They concluded that arseno-resistance is due to a modification in the biochemical properties of the spirochetes. However, they stated that this theory cannot be adopted without restriction because cases of conjugal syphilis have been observed in which only the husband or only the wife showed arsenoresistance.

On four occasions Nicolas, Lacassagne and Froment [21] have observed cases of conjugal syphilis in which both persons showed arsenoresistance, and they have found numerous reports of similar instances in the literature. They stated that arsenoresistance affecting only the husband or only the wife in cases of conjugal syphilis does occur but that the occurrence is rare. They felt that, since the only common factor in conjugal syphilis is the treponemiasis, it must be responsible for this bilateral arsenoresistance.

Bonnet [22] reported eight cases of arsenoresistant early syphilis and stated that there is an increase in the number of cases of that condition. He distinguished between cases in which improvement occurred after the first one or two injections of an arsenical but in which resistant cutaneous eruptions recurred and cases in which the disease was resistant from the beginning of treatment. He stated that arsenoresistant stumps of spirochetes would explain the resistance which manifests itself at the beginning of treatment. He said he did not think that the human organism could have changed, and he concluded that certain stumps had become more or less arsenoresistant. In the case of relapse, he considered the causative mechanism to be analogous to that of neuro-recidivism.

Jessner [23] reported six cases of arsphenamine-resistant syphilis observed in the clinic and in the private practice of Dr. Jadassohn and briefly reviewed a case which had been reported from the same clinic by Siemens. In this series of cases, conjugal syphilis occurred twice,

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20. Nicolas, J.; Massia, G., and Lacassagne, J.: Sur la fréquence croissante des syphilis arséno-résistantes dans la région lyonnaise, Bull. Soc. franç. de dermat. et syph. **35**:132-138 (Feb.) 1928.

21. Nicolas, J.; Lacassagne, J., and Froment, R.: Les syphilis novarséno-résistantes: Etude clinique et pathogénique; déductions pratiques, Presse méd. **38**:513-516 (April 16) 1930.

22. Bonnet, L. M.: Sur la fréquence actuelle des syphilis arséno-résistantes, Lyon méd. **140**:229-236 (Sept. 4) 1927.

23. Jessner, M.: Syphilis Refractory to Arsphenamine, Med. Klin. **19**:857-859 (June 24) 1923.

and two other unmarried persons were known to be infected by the same strain of pallida. Arsphenamine resistance was present in both persons in one case and restricted to one of them in two cases. This observer pointed out that in his series of cases and in many other cases of arsenoresistant syphilis which had been reported the patients did not tolerate arsphenamine well and that the eruption was frequently psoriasiform or serpiginous or occurred as seborrheic papules on the face, especially on the nose and about the corners of the mouth. Five of Jessner's patients tolerated arsphenamine poorly but reacted promptly and favorably to bismuth.

Jessner felt that in order to elucidate arsphenamine resistance the following points are important: (1) the type and localization of the lesions, (2) the patient's tolerance of arsphenamine and (3) the course of the disease in patients who have become infected with the same strain of spirochetes. He contended that when arsenoresistance occurs in cases of conjugal syphilis it is important to determine when each partner becomes infected. If both are infected at about the same time the infection may become resistant in only one; however, if the infection has become arsenic resistant in one partner before the other partner is infected, the arsenoresistance will be present in both.

Jessner suggested that probably there are several strains of arsenic-resistant spirochetes. He was unable to understand why most authorities who believed in the parasitotropic action of arsphenamine had discarded the theory that the spirochetes possessed arsenic resistance.

Lutz [24] observed four persons who were known to be infected with the same strain of S. pallida. A waitress who had moist lesions on the genitalia infected two young men, and shortly afterward the bride of one of the men became infected. The waitress who was the source of the infection and the married couple reacted favorably to neoarsphenamine and mercury. However, relapses continued to develop in the other man in spite of intensive treatment with neoarsphenamine and mercury. Finally, the relapses were prevented by the administration of silver arsphenamine. Lutz felt that in these cases all the requisites for acquiring and transmitting arsenoresistance were present, and since the same strain of spirochetes did not behave in the same manner toward arsphenamine in different persons, he concluded that the refractoriness to treatment was due to some peculiar cellular reaction of the host. He surmised that the host was incapable of converting the arsphenamine into its spirocheticidal form.

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24. Lutz, W.: Zur Kenntnis der gegen Salvarsan refraktären Syphilis, Schweiz. med. Wchnschr. **50**:838-841 (Sept. 16) 1920.

Semon [25] observed a case of primary syphilis with negative serologic reaction in which the disease reacted favorably to seven injections of an arsenical and eight injections of a bismuth preparation which were administered during the first two months of the infection. Two weeks after the last treatment a cutaneous eruption appeared which failed to respond to intensive arsenical therapy. Semon expressed the belief that arsphenamine resistance is the result of some peculiarity of the host and suggested that when it is observed the host lacks some tissue substances which are essential for the biotropic action of arsphenamine.

Although there is some experimental and clinical evidence which suggests that a strain of S. pallida may acquire an increased tolerance for arsphenamine, it is questionable whether this factor is of great importance in the production of arsenoresistant syphilis. It is more probable that arsenoresistance is a manifestation of some peculiarity of the infected organism. If this is true, one possible alteration must be a disturbance in the complicated mechanism of the action of arsphenamine, but a complete understanding of this mechanism has not been established. Arsphenamine is the most potent of modern antisyphilitic remedies; however, before its spirocheticidal effect is released the drug must undergo oxidation within the body of the host. Lee [26] has reported some experimental work which indicates that the arsenoxide of arsphenamine combines with the cellular proteins, particularly in and around the base of a syphilitic lesion. This arsenoprotein, which is poisonous to the parasite, starts retrograde changes in the spirochete, thereby making it susceptible to the protective powers of the body. It has been suggested that the arsphenamines also stimulate the production of antibodies. Moore [27] expressed the belief that this theory is not substantiated by experimental evidence.

Kolmer [28] stated that possibly part of the curative activity of arsphenamine in syphilis is due to the antigenic substances which are liberated from the disintegrated spirochetes, but he did not know of any evidence indicating that a drug is capable of increasing the defense mechanism by directly stimulating the antibody-producing tissues. Kolmer also suggested that a drug may increase the number of leuko-

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25. Semon, H. C. G.: Clinical Case: Salvarsan-Resistant Syphilis, Brit. J. Ven. Dis. **6**:323-326, 1930.

26. Lee, D. C.: Action of Arsphenamine and Mercury on the Treponema Pallidum, Am. J. Syph. **6**:546-550 (July) 1922.

27. Moore,[4] p. 68.

28. Kolmer, John A.: Principles and Practice of Chemotherapy, with Special Reference to the Specific and General Treatment of Syphilis, Philadelphia, W. B. Saunders Company, 1926, pp. 25-26.

cytes in the blood or in the area of the disease foci which may liberate enzymes, thus producing therapeutic effects.

Dale [29] stated that a new theoretical foundation of chemotherapy which embraces a more comprehensive understanding of the complex reaction within the infected host is necessary for an understanding of the mode of action of chemotherapeutic remedies. He was unable to accept Ehrlich's simple explanation of a strong affinity of the drug for the protein of the parasite and a weak affinity for the cellular protein of the host.

Gouin, Bienvenue and Ezel [30] have studied the leukocytic reaction which is produced by antisyphilitic drugs and claimed that it is of value not only as a means of diagnosis but as an aid in the selection of the most effective remedy. They found that the administration of arsphenamine, bismuth or mercury to a syphilitic person produces either leukocytosis or a leukopenia which can be demonstrated two hours after the injection. Leukopenia indicates a resistance of the infection to the drug, while leukocytosis indicates a favorable response to the remedy. These observers reported a case of arsphenamine-resistant syphilis in which there was a negative leukocytic reaction to neoarsphenamine but a positive reaction to bismuth. Psoriasiform syphilids continued to develop in spite of arsenical treatment, but the infection reacted favorably to bismuth therapy. These observations indicate that in arsphenamine-resistant syphilis there is an unusual or altered reaction of the host to the drug, and they are additional evidence that arsenoresistance is a manifestation of some peculiarity of the infected organism. This alteration may consist of inability of the reticulo-endothelial system to react to the possible stimulating action of the arsphenamine or to the antigenic substances which are liberated from the disintegrated spirochetes.

It has been known for years that in some cases of early syphilis the infection reacts unfavorably to treatment, particularly to arsphenamine therapy. Most of the reported cases have been instances in which information regarding the response to treatment of other persons infected with the same strain of spirochetes was not available. Consequently, the observation of two instances of conjugal syphilis in each of which only the wife showed arsenoresistance is of sufficient interest to warrant this report.

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29. Dale, H. H.: Chemotherapy, Physiol. Rev. **3**:359-393 (July) 1923.

30. Gouin, J.; Bienvenue, A., and Ezel, J.: Nouveau cas de syphilis arsénorésistante prévue par la leucocyto-réaction, Bull. Soc. franç. de dermat. et syph. **41**: 675-678 (April) 1934.

REPORT OF CASES

CASE 1.—A married man aged 40 was first seen on Jan. 7, 1931. His chief complaints were headache, soreness of the left eye and a generalized eruption. The only previous illness of significance was an attack of "soft chancres" in 1912. These lesions had responded favorably to cauterization and had not been followed by any of the usual signs of early syphilis. He had never received antisyphilitic treatment.

Present Illness.—The patient had noticed a sore on the penis a few weeks before the appearance of the eruption but had failed to consult a physician. He admitted having had several illicit exposures. Two or three weeks before he came under observation, he began to have severe headaches, and a generalized eruption had developed. A diagnosis of smallpox had been made, and the patient had been referred to the ward for contagious diseases of a county hospital. Soon after, he was directed to the clinic for treatment.

The initial examination revealed a well developed and well nourished man with a rather severe papulopustular type of secondary syphilis. The superficial lymph glands were palpable, and there were moist lesions on the prepuce and an iritis of the left eye. Dark field examination of material from a penile lesion showed S. pallida. The Wassermann reaction of the blood was 4 plus and the Kahn reaction 3 plus. A spinal puncture was not made.

The infection reacted favorably to intensive antisyphilitic therapy which consisted of administration of arsphenamine and a solution of a bismuth preparation in oil. Continuous treatment consisting of alternating courses of bismuth and arsphenamine were given for sixteen months. During the first seven months the patient cooperated satisfactorily, but later on he came in for treatment somewhat irregularly, and on several occasions there was an interval of two weeks between treatments. He voluntarily discontinued treatment after he had received eighteen injections (7.4 Gm.) of arsphenamine and thirty-three injections of the bismuth preparation.

After six injections of arsphenamine the iritis had disappeared and only a few of the cutaneous lesions were visible; there were no mucocutaneous eruptions while the patient remained under observation. After eleven injections of arsphenamine and thirteen of the bismuth preparation the Wassermann reaction was strongly positive, but after fifteen injections of arsphenamine and twenty-six of the bismuth preparation the Kahn reaction became negative and the Wassermann reaction of the blood weakly positive.

CASE 2.—An operator in a beauty shop aged 33 was seen first on Jan. 7, 1931. At that time the Wassermann and the Kahn reaction of her blood were negative and she had no clinical signs of early syphilis. She had helped to care for her husband (case 1) during his recent illness but had not observed any special precautions. The past history was unimportant. She had never been pregnant.

Present Illness.—In the early part of February a sore developed on the right middle finger. She thought that possibly she had injured her finger while she was at work in the beauty shop. Since the lesion did not disappear, she returned to the clinic, on March 11, 1931. There was an indurated, painless erosion on the palmar surface of the ungual phalanx of the right middle finger. The right epitrochlear and axillary lymph glands were enlarged. A dark field examination gave positive results, and the Wassermann and the Kahn reaction of the blood were both strongly positive. There were no lesions of secondary syphilis. A

diagnosis of primary syphilis with positive serologic reaction was made. It was thought that the patient had contracted the infection while she was nursing her husband during the period of his secondary eruption. No other likely source of infection could be discovered from the history.

The following outline of the treatment administered shows that the infection in this patient reacted unfavorably to antisyphilitic therapy:

Date	Treatment	Reaction
March 11	0.45 Gm. of neoarsphenamine	Severe chill, headache, nausea and vomiting eight hours later
March 14	0.3 Gm. of arsphenamine	No reaction
March 18	0.4 Gm. of arsphenamine	No reaction
March 25 to April 15	1.9 Gm. of arsphenamine	April 15, the primary lesion had practically disappeared
April 22 to May 13	4 injections of elemental bismuth in oil (total 200 mg. of elemental bismuth)	About May 1, papular syphilids appeared on the arms
May 20 to June 17	1.5 Gm. of arsphenamine; 1 Gm. of mercuric salicylate and 20 cc. of milk intramuscularly	June 2, the eruption had spread to the face and arms; psoriasiform lesions had developed; the Wassermann reaction was weakly positive; the Kahn reaction was negative
June 24 and June 27	10 mg. of colloidal mild mercurous chloride intravenously (total 20 mg.)	Lesions became more numerous; a moist infectious lesion appeared on the left side of the nose; dark field examination gave positive results; potassium iodide was prescribed
July 1 and Juyl 3	0.3 Gm. of silver arsphenamine (2 treatments)	Exudative dermatitis interpreted as a mild arsphenamine dermatitis developed on the eyelids and arms
July 7 to July 17	5 injections of ⅙ grain (0.0108 Gm.) of mercury biniodide and 0.2 Gm. sodium bismuth thioglycolate	July 17, the psoriasiform lesions were unchanged; the patient was advised to enter the hospital for protein shock; the Wassermann reaction was weakly positive; the Kahn reaction was negative; the cholesterol content of the blood was 200 mg. per hundred cubic centimeters
July 20 to July 25	Three typhoid shocks, temperature rising to 104.8 F.; patient refused to continue shock therapy	The spinal fluid was normal
July 22 to August 10	1 Gm. of sodium bismuth thioglycolate	August 10, no improvement; large psoriasiform lesions developed on the legs, arm and face; biopsy showed marked perivascular granulatous infiltration of the corium
August 21 to October 5	13 injections of ⅛ grain (0.021 Gm.) mercury biniodide and 1 grain (0.065 Gm.) mercuric salicylate	August 21, no improvement in the eruption; precocious late ulcerative syphilids appeared on the legs and arms
October 12 to November 23	3.75 Gm. of neoarsphenamine	No return of exudative dermatitis; at first some improvement in the eruption; later the lesions became more numerous
November 30 to December 7	12 cc. of colloidal mercury sulfide intramuscularly	December 7, no improvement; the Wassermann and the Kahn reaction of the blood were strongly positive

It seemed apparent that the infection would not react favorably to further antisyphilitic therapy; consequently, the patient was persuaded to take malarial treatment. At this time the examination of the blood showed 4,990,000 red cells, 4,200 white cells and 78 per cent hemoglobin. The differential count showed 67 per cent neutrophils, 1 per cent eosinophils, 29 per cent small lymphocytes and 3 per cent large lymphocytes.

Further treatment was as follows:

Date	Treatment	Reaction
Dec. 14, 1931 to Jan. 5, 1932	10 malarial chills; lowest temperature, 105 F.; highest temperature, 106.8 F.	January 5, a few lesions had disappeared; decrease in infiltration of larger lesions occurred
January 15	.....	New lesions appeared on all the extremities; the blood count showed 3,490,000 red cells, 7,250 white cells, 68 per cent hemoglobin; the differential count showed 45 per cent neutrophils, 1 per cent eosinophils, 50 per cent small lymphocytes, 4 per cent large lymphocytes
January 19 to March 9	3 Gm. of arsphenamine (7 injections) and 3 injections of an oil-soluble bismuth preparation	The infection reacted favorably to treatment; by February 15, the eruption had practically disappeared; mild arsphenamine dermatitis developed on February 25; arsenic medication was discontinued
March 20 to October 24	15 injections of 1 cc. of 1 per cent solution of mercuric chloride; 12 injections of sodium bismuth tartrate; inunctions of mercury for one month	The patient was less cooperative; came in irregularly for treatment; the Wassermann and the Kahn reactions were weakly positive on June 10, 1932

Summary.—In this case, treatment was started during the seropositive primary stage of the infection. The primary lesion reacted favorably to arsphenamine, but three weeks after the termination of the first course of arsphenamine, papular syphilids began to appear on the extremities (fig. 1). The eruption spread to the face; the lesions became psoriasiform, and precocious ulcerative syphilids developed on the arms and legs within the first seven months after the onset of the disease. Psoriasiform and gummatous syphilids persisted in spite of approximately ten months of continuous treatment with arsphenamine, bismuth, mercury and potassium iodide and a limited amount of foreign protein therapy. The infection was not only arsphenamine-resistant but failed to respond to other antisyphilitic remedies. This is an example of the rare type of drug-resistant syphilis.

Finally the patient was inoculated with the parasite of tertian malaria and allowed to have ten paroxysms of fever. Malarial therapy did not cause the eruption to vanish; however, some of the smaller lesions disappeared, and the infiltration in others decreased. This improvement was not permanent. Ten days after the termination of the malaria new psoriasiform syphilids began to appear on the extremities, but the drug-resistant properties of the infection had been removed, as manifested by a practically complete disappearance of the eruption after administration of seven injections of arsphenamine. Unfortunately, a mild arsphenamine dermatitis developed after the last injection which made it necessary to continue the treatment with bismuth and mercury. The patient became less cooperative and voluntarily discontinued treatment. There had been no mucocutaneous recurrence during the last eight months the patient was under observation.

Case 3.—A married man aged 33 was first seen on Oct. 23, 1933. He had contracted gonorrhea in 1932, and on several occasions small "sores" had developed on the prepuce. These lesions usually disappeared within two or three days. In January 1933 the Wassermann reaction of the blood was negative. Otherwise the past history was irrelevant.

Present Illness.—On November 21 the patient noticed a small lesion on the penis. He had been married four months and said he had not had extramarital coitus; therefore, he was requested to bring his wife in for an examination.

The patient was a well developed man. The physical examination gave negative results except for the presence of an indurated lesion the size of a split pea on the prepuce. There was a superficial oval erosion of the central portion of the lesion. There were enlarged lymph glands in the left inguinal region. A dark field examination showed S. pallida. The Wassermann and the Kahn reaction

of the blood were negative. Examination of the blood showed 4,480,000 red cells, 7,050 white cells and 76 per cent hemoglobin.

A diagnosis of seronegative primary syphilis was made, and intensive treatment was instituted.

Treatment was of the continuous type, consisting of alternating courses of an arsenical and of a heavy metal. The patient remained under observation for ten months, and during this period he received five injections of arsphenamine, seventeen of neoarsphenamine and twenty-two of bismuth subsalicylate. The chancre reacted favorably to treatment; there were no mucocutaneous recurrences, and the serologic reaction remained negative. The patient did not submit to a spinal puncture and voluntarily discontinued treatment.

Fig. 1 (case 2).—Corymbiform lesions on the knee and a nodular ulcerative lesion on the side of the knee.

Case 4.—A woman aged 25 was first observed on Oct. 24, 1933. She did not feel ill and came in for examination because her husband (case 3) had discovered that he had contracted syphilis. She had been married twice and in 1930 had contracted gonorrhea after her first marriage. She married her present husband in July 1933. The past history was irrelevant.

Present Illness.—There had been no recent constitutional or subjective symptoms, and the patient was noncommittal regarding the source of her infection. She was well developed and well nourished. With the exception of the cutaneous lesions, a general physical examination did not reveal any noteworthy findings. There were a few small light red, slightly infiltrated, flat, smooth papules scattered over the body and on the extremities which had been present only a day or so. There were a few small moist papules on the vulva, and on the right large labium there was an infiltrated pea-sized papule with an eroded surface. The lymph

glands in the right inguinal region were enlarged. The mucous membranes of the mouth were free from lesions. A dark field examination of material obtained from a vulvar lesion showed S. pallida, and the Wassermann and the Kahn reaction of the blood were strongly positive. Examination of the blood on admission showed 3,750,000 red cells, 5,200 white cells and 71 per cent hemoglobin.

A diagnosis of secondary syphilis was made. The patient had never been pregnant, although she thought she was pregnant at this time as her menstrual period was about three weeks overdue.

The following outline shows that the infection in this patient was more resistant to the arsenicals than in the average person.

Date	Treatment	Reaction
Oct. 24, 1933 to October 30	0.55 Gm. of arsphenamine (3 treatments)	Nausea and vomiting occurred after each injection; patient was sick for several hours
November 1	.....	A generalized, scarlatiniform eruption, probably an "erythema of the ninth day" described by Milian, developed on October 31, the day following the last injection of arsphenamine, but this was not recognized at that time; consequently, bismuth was given at the next two visits
November 3 and November 8	2 grains (0.13 Gm.) of bismuth subsalicylate	November 3, secondary eruption had faded considerably
November 10 to December 4	0.6 Gm. of silver arsphenamine (4 treatments)	November 10, the eruption returned; many new lesions appeared; psoriasiform lesions developed; nausea and vomiting occurred four or five hours after each injection; the patient was sick for several hours
December 11	2 grains (0.13 Gm.) of bismuth subsalicylate	The eruption remained unchanged; the diagnosis of pregnancy was established
December 16 to December 28	1.5 Gm. of neoarsphenamine; 15 cc. milk protein (3 treatments)	December 28, no change in the eruption; many psoriasiform lesions appeared; no reaction occurred after neoarsphenamine
Jan. 4, 1934	Biopsy	Dark field examination of material from the margin of the biopsy wound showed S. pallida
January 3 to January 6	4 injections of 1/6 grain (0.108 Gm.) of mercury succinimide	The Wassermann and the Kahn reactions were strongly positive
January 6 to January 27	18 inunctions of mercury	January 27, some improvement was noticeable at the end of the course of inunctions; however, many lesions were still present
January 27 to February 9	1.8 Gm. of neoarsphenamine (3 treatments)	Nausea and vomiting for three or four hours after each injection, consequently arsphenamine was substituted; no change in the eruption after administration of neoarsphenamine
February 16 to March 16	1.2 Gm. of arsphenamine and 6 grains (0.39 Gm.) of bismuth subsalicylate (4 treatments)	By March 16, there was slight improvement, a few lesions had disappeared but many remained unchanged
March 23 to April 13	5 injections of a bismuth preparation each containing 2/3 grain (0.024 Gm.) of colloidal metal	Marked improvement after fifth injection of colloidal bismuth preparation; however, eruption had not completely disappeared
April 18 to June 26	4 grains (0.26 Gm.) of bismuth subsalicylate (2 treatments), 2.1 Gm. of arsphenamine (7 treatments)	Continued improvement; no eruption was present on April 25; there were no further recurrences; the blood count showed 3,930,000 red cells, 7,750 white cells and 71 per cent hemoglobin
June 29	.....	The Wassermann and the Kahn reactions were strongly positive
June 30	.....	The patient was confined; the Wassermann and the Kahn reactions of blood obtained from umbilical cord were negative; the Wassermann and the Kahn reactions of the child's blood were negative on Aug. 17, 1934; after her confinement the patient received four injections of bismuth subsalicylate and then discontinued treatment
April 16, 1936	.....	The child was observed but showed no signs of congenital syphilis; the Wassermann and the Kahn reaction were negative

Summary.—In this case, treatment was started early in the secondary stage of the infection. As in case 2 the initial treatments produced some fading of the lesions, but later secondary syphilids became more numerous and the eruption became psoriasiform. Since the patient was pregnant it was thought advisable to give arsenical therapy in preference to treatment with the heavy metals, even though the arsphenamines were not well tolerated. During the first nine weeks, treatment consisting of 0.55 Gm. of arsphenamine, 0.6 Gm. of silver arsphenamine, 1.5 Gm. of neoarsphenamine and 6 grains (0.39 Gm.) of bismuth subsalicylate failed to produce any improvement in the eruption, and at the end of this period motile spirochetes were obtained from the lesions. For two more months treatment was continued, consisting of inunctions of mercury, 6 grains of bismuth subsalicylate, 1.2 Gm. of neoarsphenamine and 1.2 Gm. of arsphenamine and at the end of that period psoriasiform lesions were present. However, many lesions had disappeared. Continuous treatment for five months was relatively ineffective. The eruption gradually disappeared after a course of injections of a colloidal preparation of bismuth. This patient had an arsenoresistant psoriasiform type of

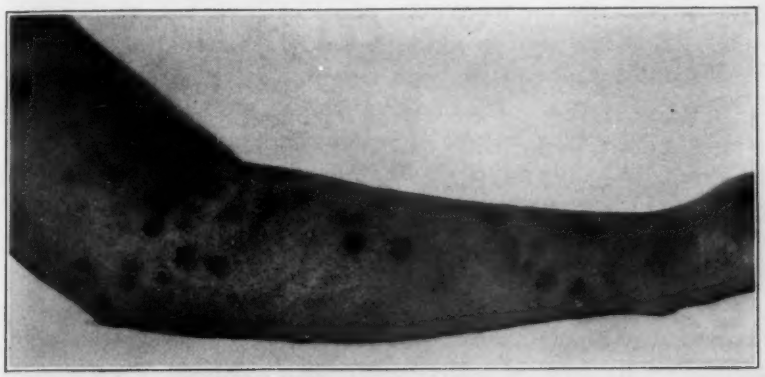

Fig. 2 (case 4).—Resistant psoriasiform syphilids.

secondary syphilis caused by the same strain of S. pallida as that which had produced in her husband a seronegative primary infection which reacted favorably to treatment. The arsenicals were tolerated poorly by this patient; consequently the amount of the drug which was administered at various times never exceeded the minimum dose recommended for women. This may partially account for the resistance to treatment in this case; however, the infection failed to react as favorably to treatment as early syphilis usually does or as favorably as the infection of the husband.

COMMENT

Cases 1 and 3, in which an early syphilitic infection reacted favorably to treatment, are of interest only because in each case the patient presumably was infected with the same strain of S. pallida as that which produced a resistant infection in the respective marital partner. Case 2 may be considered as an example of the rare type of drug-resistant syphilis, while in case 4 the reaction to the arsphenamines was definitely less favorable than that observed in cases of ordinary acute syphilis. Case 4 is also of interest because of the concept that pregnancy exerts an

inhibitory effect on a syphilitic infection. Stokes [31] stated that pregnancy and lactation are influential in reducing the severity of syphilis in women. Wile and Shaw [32] felt that it is a fairly well established fact that pregnancy apparently aids the syphilitic defense mechanism in the mother. Brown and Pearce [33] have shown that in pregnant and lactating rabbits inoculated with the organisms of syphilis primary lesions did not develop as frequently as in nonpregnant animals. Ingraham and Kahler [34] recognized that the visceral lesions of syphilis are less common in women, but they expressed doubt that pregnancy has an ameliorating effect on the course of the disease. They referred to Fournier's observation that a marked increase in size and severity of primary and secondary lesions of the genitalia may occur during pregnancy. The Cooperative Clinical Group [35] concluded that the amount of treatment administered and the stage of the infection at the time treatment is started are more important factors than pregnancy in controlling the clinical course of the disease. Their studies indicate that pregnancy protects the patient with early syphilis against an involvement of the nervous system. Halloran [36] expressed the belief that pregnancy alters the clinical manifestation of syphilis in that primary and secondary lesions are frequently either absent or mild, and he suggested that this may explain why so many pregnant women who have a positive Wassermann reaction are unable to recall having had primary or secondary lesions.

Moore [4] stated that pregnancy exerts an important influence on the course of a syphilitic infection and that when the impregnation and the acquiring of the infection coincide, the manifestations of early syphilis may be suppressed completely or, if they develop are usually milder than

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31. Stokes, John H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1928, p. 24.

32. Wile, Udo J., and Shaw, J. W.: The Prenatal Treatment of Syphilis with Especial Reference to Early Syphilis in the Mother, J. A. M. A. **95**:1791-1795 (Dec. 13) 1930.

33. Brown, W. H., and Pearce, Louise: Reaction of Pregnant and Lactating Females to Inoculation with Treponema Pallidum: A Preliminary Note, Am. J. Syph. **4**:593 (Oct.) 1920.

34. Ingraham, Norman R., Jr., and Kahler, James E.: Diagnosis and Treatment of Syphilis Complicating Pregnancy, Am. J. Obst. & Gynec. **27**:134-152 (Jan.) 1934.

35. Cole, H. N.; Moore, J. E.; O'Leary, P.; Stokes, J. H.; Wile, U. J.; Clark, T.; Parran, T.; Vonderlehr, R. A., and Usilton, L. J.: Cooperative Clinical Studies in the Treatment of Syphilis: Syphilis in Pregnancy, J. A. M. A. **106**:464-467 (Feb. 8) 1936.

36. Halloran, C. R.: Syphilis and Pregnancy: Effect, Diagnosis, Treatment and Complications with Report of Unusual Nitritoid Crisis, Am. J. Syph. & Neurol. **14**:222-230 (April) 1930.

in nonpregnant women or in men. Moore also stated that pregnancy influences favorably the ultimate outcome of a syphilitic infection only in cases in which pregnancy occurs after infection has become latent. In case 4, impregnation and the infection probably occurred simultaneously; however, the infection was uninfluenced by the usual inhibitory action of pregnancy. This observation may be interpreted as another indication that in that case the resistance or severity of the infection was a manifestation of an alteration in the biologic properties of the host.

There is no way of proving that two patients are infected with the same strain of spirochetes; however, such an assumption is justified in cases of conjugal syphilis. Obviously, the arsenoresistance in the wives in the two instances of conjugal syphilis which are described was not the result of the inefficacy of the drug or of an alteration in the biologic properties of the spirochetes but was the result of factors inherent within the hosts. With the exception of silver arsphenamine the same arsenical preparations which were used in the treatment of the husbands were administered to the wives.

Little is known regarding the nature of the alterations within the host which are factors in the production of drug-resistant syphilis. The elucidation of this complex problem is dependent on the solution of the mechanism of the action of antisyphilitic remedies as well as on a more comprehensive understanding of the rôle played by the defense mechanism of the host in combating a syphilitic infection. Many observers have assumed that arsenoresistance is the result of the inability of the host to change the complex arsphenamines into their spirocheticidal arsenoxide components or that the arsenoprotein which is formed within the host is nontoxic to the spirochetes. Unfortunately the new arsenoxide, mapharsen, which has recently been introduced in this country was not available while the cases reported were under observation.[37] A resistance of early syphilis to this arsenical would indicate that arsenoresistance is partly the result of an altered arsenoprotein which is formed within the host, and a favorable reaction in cases in which the disease was resistant to arsphenamine would indicate that the host was unable to oxidize the arsphenamines properly. That a depression or alteration in the natural defense mechanism may be an important factor in arsenoresistance is suggested by the observation that procedures which are thought to stimulate immunologic processes and to mobilize antibodies, such as induced hyperpyrexia and foreign protein shock therapy, cause the arsenoresistant characteristics of the infection to disappear.

37. Foerster, O. H.; McIntosh, R. L.; Wieder, L. M.; Foerster, H. R., and Cooper, G. A.: Mapharsen in the Treatment of Syphilis: A Preliminary Report, Arch. Dermat. & Syph. **32**:868-889 (Dec.) 1935.

The severity of the clinical manifestation of any infectious disease is dependent on the virulence of the virus and on the efficiency of the natural defense mechanism of the host. In untreated early syphilis the lesions disappear, and the asymptomatic or latent stage of the disease is established as a result of the activity of the patient's defense mechanism. There is ample experimental and clinical evidence to show that the defense reaction in the tissues of the patient is an important factor in the ultimate outcome of cases of treated early syphilis. For example, it is now recognized that early neurorecurrences are the result of a suppression of the defense mechanism of the patient during the early stages of the infection by inadequate and injudicious use of arsphenamine rather than the result of a neurotropic strain of S. pallida. It is reasonable to assume that the efficiency of the natural defense reaction as well as the degree of its susceptibility to the depressing action of chemotherapeutic agents varies with patients. It is possible that this individual variation in the reaction of the tissues of the host to the antigenic substances of the spirochetes materially influences the end-results of antisyphilitic therapy. Presumably, in a person with syphilis resistant to arsphenamine or to other drugs there is either inability to metabolize the drug properly or lack of stimulation of the defense mechanism of the body by S. pallida. It is possible that both of these factors are important in the production of drug resistance. I have been unable to find reports of observations made in cases of arsphenamine-resistant syphilis which prove that the infected persons were unable to oxidize arsphenamine or that the arsenoproteins which were formed were innocuous to the spirochetes. The opinion that there is an alteration in the metabolism of arsphenamine in arsenoresistant syphilis is nothing more than a logical deduction based on the present concept of the mechanism of the action of arsphenamines.

Recently more attention has been given to the importance of the defense of the body against a syphilitic infection, and measures which are thought to stimulate immunity are being more generally used in resistant early and late somatic syphilis.[38] Dennie [39] expressed the opinion that too much attention has been given to the chemical treatment of syphilis. He aptly said, "Nearly all of our energy has been directed toward finding a remedy that will kill the spirochete, the cause of the disease, and very little toward bettering the condition of the individual who has within his tissues the same organism." He felt that the reticulo-endothelial system provides the natural defense of the body against

38. Dennie, C. C., and McBride, W. L.: Treatment of Resistant Somatic Syphilis, Arch. Dermat. & Syph. **30**:1-5 (July) 1934.

39. Dennie, C. C.: Method of Increasing Specific Resistance of Syphilitic Individual to His Disease, South. M. J. **25**:462-467 (May) 1932.

syphilis and that the plasmodium of malaria acts as a powerful stimulator of this system; consequently, the macrophages derived from vascular endothelium and other defense units of this system which are formed in response to the irritative action of the spirochetes are made more active by the action of the malaria parasite. These cells are thought to act by devouring the spirochetes.

The disappearance of the arsenoresistance after nonspecific therapy suggests that the activity of the defense mechanism of the host is an important factor which influences the response of a syphilitic infection to chemotherapeutic agents. This assumption is based on the present concept of the mechanism of the action of fever therapy.

There is a voluminous literature dealing with the various phases of this problem:

Hench, Slocumb and Popp [40] recently enumerated the physiologic reactions produced by fever therapy and stated:

> The benefits of fever therapy presumably arise from: (1) a direct bacteriolytic or bacteriostatic effect due to the influence of heat itself on bacteria . . ., (2) an indirect bacteriolytic or bacteriostatic effect resulting from increasing formation or mobilization of immune bodies, (3) a local effect from vasodilatation, providing an augmented blood supply to the inflamed tissues, and (4) a general effect from the heightened metabolism incident to fever.

Dennie, Polsky and Lemoine [41] expressed the belief that a temperature of 105 F. has a spirochetostatic rather than a spirocheticidal effect and that the defense mechanism of the body is most active after a temperature of 104 F. has been reached. They stated that the spirochete does not die a thermal death but that its virility is decreased by the reaction of the host, which makes it more susceptible to the stimulated immune forces of the body. They expressed the opinion that hyperpyrexia is of little value in early syphilis because in the majority of cases the patient is already receiving the benefits of a high degree of stimulation of the defense mechanism of the body; however, in cases of early syphilis with a prematurely negative serologic reaction and in cases of the so-called malignant syphilis fever therapy is of value as a means of stimulating an inactive defense mechanism. These observers reported a case of late secondary syphilis of the ulcerative type in which the general condition of the patient was greatly improved and the ulcers were completely healed by fever therapy. They concluded that the improvement in this case resulted from the stimulation of the immunologic forces of the body.

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40. Hench, P. S.; Slocumb, C. H., and Popp, W. C.: Fever Therapy: Results for Gonorrheal Arthritis, Chronic Infectious (Atrophic) Arthritis and Other Forms of "Rheumatism," J. A. M. A. **104**:1779-1790 (May 18) 1935.

41. Dennie, C. C.; Polsky, M., and Lemoine, A. N.: Hyperpyrexia Produced by the Hot Bath in the Treatment of Syphilis, J. Missouri M. A. **33**:1-12 (Jan.) 1936.

The occurrence of arsenoresistance in one of the marital partners in each case in this series precludes the incrimination of the spirochete, as it is doubtful that the virulence of the infecting organism could have been increased greatly by a single transfer. In case 1 a strain of S. pallida produced secondary syphilids which reacted favorably to arsphenamine and the heavy metals; yet, the same strain of organisms presumably produced in another person (case 2) a psoriasiform type of secondary syphilis and precocious gummatous lesions which were uninfluenced by arsphenamine, bismuth and mercury. In the second couple, only the wife showed arsenoresistance. In each case in which there was resistance to treatment, motile spirochetes were demonstrated in the cutaneous lesions after several weeks of continuous therapy. In both cases the eruption was of the psoriasiform type, and each of the two patients reacted poorly to the arsenicals. This is of interest because Moore and Robinson,[2] Jessner [23] and others have observed that psoriasiform syphilid is frequently arsphenamine resistant. It is obvious that the drug resistance exhibited by the wives in the cases reported here was the result of peculiar alterations within the bodies of the women.

In case 2 these alterations within the host were removed by malarial therapy. Most authorities agree that one of the beneficial effects of malarial treatment in certain types of syphilis is derived from the stimulating action of the parasite on the defense mechanism of the body. Therefore it is reasonable to assume that one peculiarity of the host in cases of drug-resistant syphilis is the lack of stimulation of the defense mechanism of the body by the spirochetes or the products of their disintegration.

Why the arsenoresistant characteristics of a syphilitic infection disappear after fever therapy is not known; however, it is doubtful whether the phenomenon can be explained entirely as a combination of a decrease in the virility of the spirochetes and a stimulation of the defense mechanism of the host. It is possible that the heightened metabolism incident to the fever may produce an alteration in the body which enhances the ability of the patient to metabolize arsphenamines which are subsequently administered, because after fever therapy the lesions of resistant syphilis react as favorably to arsphenamine as do the lesions in cases of ordinary nonresistant syphilis.

The fact that the drug-resistant properties of a syphilitic infection disappear after fever therapy is not only of interest theoretically but of great importance practically. By the use of hyperpyrexia followed by intensive antisyphilitic therapy the prognosis is greatly improved, and the menace to the public health is decreased to the level of the risk caused by the average patient with acute syphilis who is receiving similar antisyphilitic treatment.

Moore and Robinson [2] have observed that resistance to arsphenamine is usually specific for one member of the arsphenamine group or for one group of antisyphilitic remedies, and they stated that it is exceedingly rare for the lesions to be resistant to all preparations of arsphenamine and to bismuth and mercury. Miller's patient showed a resistance only to arsphenamine. That resistance is usually specific for one particular drug or group of drugs has been observed by others; consequently, the management of drug-resistant syphilis has consisted mainly of a change in treatment, neoarsphenamine or silver arsphenamine being used in the case of arsphenamine resistance and bismuth and mercury in cases in which a resistance to all arsenicals was evident.

In view of present knowledge, such a regimen may be justified in cases in which resistance is limited to a single drug. However, when there is resistance to a group of drugs, particularly to the arsenicals, which are the most potent spirocheticidal of antisyphilitic remedies, it is necessary to resort to fever therapy. After such therapy has been administered the infection reacts favorably to the arsphenamines, and the possibility of obtaining a clinical and serologic cure is greatly enhanced.

SUMMARY

Two instances of conjugal syphilis of the early type in each of which only the wife showed drug resistance are reported. In one case the infection was resistant to the arsenicals and to bismuth and mercury while in the other the infection was resistant to three of the most commonly used arsenicals. A resistance to both arsenic and the heavy metals tends to invalidate the theory of an arsphenamine-resistant strain of S. pallida. In each case spirochetes were present in the cutaneous lesions several weeks after antisyphilitic therapy had been instituted.

The observation of Moore and Robinson, Jessner and others that persons with arsenoresistant syphilis usually tolerate arsphenamine poorly and frequently exhibit psoriasiform lesions is well exemplified by the two cases reported here.

It is of interest that the drug resistance in this series of cases occurred in the women, the sex in which the early manifestation of syphilis is prone to be mild or absent and that in one of the women a pregnancy, the onset of which coincided with the acquiring of the infection, failed to exert an inhibitory action on the disease. It is possible that arsphenamine so depressed the defense mechanism of the body that this patient (case 4) was deprived of the usual beneficial effects of pregnancy or that, as she exhibited a poor tolerance for arsphenamine, too small amounts of the drug were given early in the disease to prevent the spirochetes from acquiring some degree of tolerance to the drug or from becoming more thoroughly entrenched. The last assumption is hardly

tenable in view of the fact that in the other woman (case 2) arsenoresistance developed in spite of intensive arsphenamine therapy which was administered during the early stage of the infection.

The drug resistance existing in only one of the marital partners which was observed in each of these two cases cannot be explained on the basis of an arsphenamine-resistant strain of S. pallida or as a result of a decrease in the spirocheticidal activity of the drug which was administered. The host must be incriminated.

Practically nothing is known regarding the nature of the alterations within the host which contribute to the production of arsphenamine or drug resistance in early syphilis. Many observers feel that the infected person is unable to metabolize arsphenamine properly, while others think that the tissues which are responsible for the natural defense reaction are not stimulated by the spirochetes. It is possible that both factors contribute to the production of arsenoresistance.

In one case the resistance of the infection to arsphenamine, bismuth and mercury disappeared after malarial therapy.

This beneficial effect of fever therapy presumably arose from the following factors: (1) the decrease in virility of the spirochetes by direct action of heat, (2) the stimulation of the body defense mechanism of the patients and (3) an increase in metabolism incident to fever which may have produced alterations within the host, thus facilitating the metabolism of arsphenamine which was subsequently administered.

CONCLUSIONS

There are few reports of arsphenamine-resistant syphilis in the American literature; however, during the past decade, numerous cases have been reported in the French and German literature. There is no satisfactory explanation for the apparent increase of arsenoresistant syphilis in Europe.

There is a diversity of opinion as to whether arsenoresistant syphilis is due to a decrease in the spirocheticidal activity of the drug, alterations in S. pallida or some peculiarities of the host. The mechanism of drug resistance remains unsolved; however, the two instances of arsenoresistance in one marital partner in the cases of conjugal syphilis reported here indicate that the resistance is due to alterations within the host.

The drug-resistant characteristic of a syphilitic infection disappears after fever therapy; therefore, hyperpyrexia should be induced—preferably by inoculation with the malaria parasite—as soon as the existence of drug resistance has been established.

After the fever therapy the infection reacts favorably to arsphenamine and the heavy metals.

ABSTRACT OF DISCUSSION

DR. JOHN ERIC DALTON, Indianapolis: To judge the incidence of arsphenamine-resistant syphilis solely by the frequency of reports may lead to false conclusions. One may ask whether in Europe the more numerous reports have stimulated the medical profession to closer recording of cases, for a comparison of personal experience in this country with experience in Jadassohn's clinic seems to indicate that that kind of syphilis is equal.

Certain observations in cases of this complex become interesting when compared to similar observations in cases of other conditions. Leukopenia following the administration of antisyphilitic drugs is cited as a probable sign of resistance to the drug administered. Leukopenia in lupus erythematosus is regarded as a signal of intolerance to therapy with a gold compound. Can leukopenia suggest both hypersensitivity and resistance? Both hypersensitivity and resistance are noted oftener to the arsphenamines than to the other antisyphilitic drugs, and drug-resistant syphilis frequently clears when the therapy is changed to administration of the more generally tolerated heavy metals. Can the poorer response to arsphenamine reported in these cases of drug-resistant syphilis indicate some hook-up between resistance and intolerance? Can an intermediate factor be at play between the drug introduced and the resistance of the patient's infection to that drug? Keining expressed the belief that in certain persons ingestion of salt leads to a disturbance in mineral equilibrium which so alters the vegetative nervous system that vegetative dermatosis results. Bommer further expressed the opinion that by reestablishing proper mineral balance favorable results are obtainable in conditions associated with the presence of pathologic changes in the vessels. Does sodium act in this irritant manner only in persons who congenitally or temporarily possess an unstable vegetative nervous system? Can arsenic introduced into the patient with a disturbed vegetative nervous system produce a similar reaction? Can arsphenamine-resistant syphilis due to an altered vegetative nervous system be associated with a vascular change which retards involution by blocking the entrance of the drug into the lesion? A case illustrating some of these factors is cited: A patient with seronegative primary syphilis was given treatment with the lately introduced arsenoxide by a competent urologist. After the seventh injection a sparse psoriasiform eruption developed and the primary eruption reappeared. The Wassermann reaction became frankly positive. In consultation it was additionally noted that the patient exhibited cyanotic extremities, hyperhidrosis and dermatographism, and the history revealed that the patient had been carrying a heavy occupational responsibility over a prolonged vacationless period. Five weeks of combined neoarsphenamine, bismuth and iodide therapy failed to bring about improvement. Vacation from work with continuance of the same therapy was advised, and after two weeks the lesions had markedly involuted.

DR. ARTHUR W. STILLIANS, Chicago: I am acting on the suggestion made by Dr. Dalton that cases of arsphenamine-resistant syphilis should be reported. At the clinic of the Northwestern University my colleagues and I have been interested in the study of the effect of heat on untreated syphilis, and we found that the most intensive treatment with hyperpyrexia that we dare to give has no effect in stopping the progress of syphilis. On the other hand, a patient with arsphenamine-resistant syphilis recently presented himself. After having received fifteen doses of neoarsphenamine he still had active spirochetes in his lesion, but a few treatments with hyperpyrexia followed by doses of neoarsphenamine no larger than those previously given promptly destroyed the spirochetes, and to date there has been no recurrence. The case will be reported in detail by Dr. Neymann and Dr. Lawless.

Dr. Harry M. Robinson, Baltimore: While doing some work on arsphenamine-resistant syphilis I reviewed seven thousand or more cases of early syphilis and encountered about fifteen cases of the arsphenamine-resistant form of the disease. Study of these fifteen cases revealed certain facts. Only one patient, a man, required fever therapy. In this patient the reason for the resistance was probably the fact that the patient could not tolerate any of the arsphenamines except mapharsen, all the others creating so marked a reaction that they had to be discontinued. Apparently mapharsen was not sufficiently effective; lesions continued to appear, and pallida could be demonstrated in them. Administration of the fever therapy caused the lesions to disappear, and they did not recur after the therapy with mapharsen was resumed. One of the patients was a 3 month old child with congenital syphilis who had condylomata lata in which S. pallida could be demonstrated for eight weeks during which treatment was given. During four weeks the patient received sulfarsphenamine and during the other four he received treatment with sulfarsphenamine and bismuth. When inunctions of mercury were added to these methods of therapy, the lesions involuted and the S. pallida disappeared. My impression is that arsphenamine-resistant syphilis is purely an individual reaction; that is, the obstinacy is not in the disease but in the patient's reaction to therapy and to syphilis, and in all but the aforementioned case I have been able to control the syphilis and cause involution of the lesions by merely combining or changing therapy.

Dr. E. W. Netherton, Cleveland: I was glad to hear both Dr. Dalton and Dr. Robinson refer to cases of resistant syphilis in which the new drug, mapharsen, was used. That was not available at the time the cases I reported were under observation. The fact that the arsphenamine resistance does not disappear when mapharsen is being used seems to indicate that faulty metabolism of arsphenamine is probably not an important factor in the causation of arsenoresistant syphilis. I have classified one case (case 2) as one of rare drug resistance and the other (case 4) as plain arsphenamine or arsenic resistance. I feel that cases of treatment-resistant syphilis should be reported and that one should study the host or patient more carefully, because apparently the host and not the drug or organism is at fault.

Dr. Dalton brought up the question of the relationship between intolerance and arsenoresistance. I am not prepared to comment on his suggestion as to the cause of arsenoresistance. However, intolerance to arsenic and arsenoresistant syphilis are frequently associated. In fact, all the patients with arsenoresistant syphilis, or a large number of them, tolerated the drug poorly.

ADENOMATOID SEBACEOUS TUMORS, WITH PARTICULAR REFERENCE TO ADENOMATOID HYPERPLASIA

ROBERT LOUIS GILMAN, M.D.
PHILADELPHIA

It is well known that there develop on the face (rarely elsewhere) certain small yellow and slightly elevated noninflammatory lesions which are not milia but have a composition essentially like that of sebaceous glands. They are commonly regarded as sebaceous nevi. They progress slowly over a period of years and occur most frequently in persons over 40. Interest centers largely around their pathology. Some of the lesions are congenital and can be regarded only as nevi. Others, apparently developing later in life, on the basis of analogy with the history of pigmented moles may also be regarded as (sebaceous) nevi. However, the evidence of nevic origin is not nearly so convincing for such sebaceous lesions as for pigmented moles because the architecture of the former is clearly that of a highly organized structure which is normal to the skin—which is not true of pigmented nevi.

A state of confusion exists concerning both sebaceous tumors and sebaceous hypertrophy. It is due in large measure to synonymy and nomenclature and to the failure to correlate or evaluate the histologic observations. Likewise there is a looseness in the use of the term adenoma as well as a difference of opinion as to what constitutes a true nevic state. To obtain evidence of this one need but consult any of the half-dozen recognized textbooks or note the lack of unanimity in the discussions following the presentations of papers or of cases representative of disorders of this group. Any confusion existing in clinical diagnosis may be attributed in no small measure to the lack of biopsy. This in turn may well be due to the fact that often lesions such as those under consideration are regarded as quite banal; moreover, because of their usual location the clinician hesitates to propose a means of diagnosis that might eventually result in a scar. Furthermore in my experience these various sebaceous lesions are not as common as one has been led to believe. The advisability of making a biopsy is shown by the fact that it is not unusual to observe malignant changes in growths which clinically were regarded as innocent. The dividing line clinically is not always sharp.

From the Laboratory of Dermatological Research, University of Pennsylvania.

Read at the Fifty-Ninth Annual Meeting of the American Dermatological Association, Inc., Swampscott, Mass., June 5, 1936.

Interest centers on the growths variously denominated adenoma sebaceum (Pringle), sebaceous adenoma (Balzer), senile sebaceous gland nevi, naevus sebaceus (Jadassohn) and simple sebaceous hyperplasia. Various other synonymical terms are not considered, and other conditions, such as steatoma, Fordyce's disease and multiple benign cystic epithelioma are not discussed.

In the conditions under consideration attention centers mainly on the group of indeterminate lesions which have been classified both as nevic and as simple hyperplastic disorders. In an attempt at simplification it is possible to arrange practically all the benign lesions into one of three categories:

Nevi:
- Naevus sebaceus (Jadassohn)
- Other sebaceous lesions with nevic characteristics

Adenomas:
- Adenoma sebaceum (Pringle)
- Sebaceous adenoma (Balzer)

Hyperplastic Disorders:
- Simple adenomatoid hyperplasia (synonyms, senile sebaceous gland nevi and senile sebaceous adenoma)
- Rhinophyma

HISTOLOGY

The problem of sebaceous nevi has been discussed in detail by Dietel.[1] The illustrations which accompany his article emphasize the fact that such sebaceous lesions even when present at birth exhibit a structure indistinguishable from that of normal sebaceous glands. Therefore an examination of single sections may add little if any information as to the pathogenesis of the disorder. The subject has also been presented in a complete review by Robinson.[2] Incidentally, the claims of Kyrle quoted therein that an atrophy or absence of basal cells in the sebaceous lobules connotes a nevic process is open to question. Such changes could be the result of pressure atrophy incident to the marked dilatation of the lobules. Similar changes are likewise observed in rhinophyma, which surely is not a nevic disorder. To simplify the matter one may say that in order for a lesion to qualify as genuinely nevic it must show either obviously nevic cells or a nevic construction as illustrated by a true congenital arrest with a purposeless arrangement of the sebaceous lobules. It is true that the lack of orderly placement may be seen likewise in adenomatous states, but such disorders occur later in life. To regard as a sebaceous nevus any sebaceous growth

1. Dietel, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3.

2. Robinson, S.: Naevus Sebaceus (Jadassohn), Arch. Dermat. & Syph. **26**:663 (Oct.) 1932.

which in a single section is apparently made up of hypertrophic gland elements which are disorderly in the sense that there is no apparent connection with the surface when no other nevic criteria are present is an erroneous premise. By employing wax reconstructions glands may be proved to be functionally active and to have surface openings.

True sebaceous adenoma as it is known occurs later in life. In such lesions besides the adenomatous arrangements of the sebaceous gland elements with varying increase in size and number of the glands there is hyperplasia of the blood vessels or connective tissue. In certain instances fibrous encapsulation may occur. According to the predominating tissue the lesions are classified as belonging to the Balzer type (preeminently glandular), the more multiple type of Pringle characterized by increase in the blood vessels (evidenced clinically by telangiectasia) and the less well known entities described by Hallopeau as fibrous nevi together with those described by Darier as of a fibroangiomatous type. In Pollitzer's [3] case, the first reported in this country, there were in addition to cystic degeneration certain peculiar epithelial structures undergoing colloid change and suggesting sweat gland apparatus in appearance but not in location. Some investigators exclude the Balzer type and classify that disorder with the benign adenoid epitheliomas.

The histologic changes in true (simple) sebaceous hyperplasia are similar in certain respects to those in sebaceous nevi and in adenoma. Glandular hyperplasia and hypertrophy are present, with possibly an increase of connective tissue, with or without changes in the elastic tissue. (Patients with sebaceous hyperplasia are uniformly older than those with sebaceous nevi and adenoma.) There are lacking, however, the requisite nevic signs stated; while the picture may still be termed adenomatoid there exists no evidence of true adenoma. The glandular elements are not disorderly in their arrangement, since detailed study can demonstrate connections between them and ducts which finally open on the surface. In addition to these changes I have noted consistently in cases of sebaceous hyperplasia the presence of Demodex folliculorum in numbers too large to be interpreted as other than abnormal, and this circumstance directs attention to a possible explanation of the existing increase in glandular function.

These more or less involved problems of classification were presented in connection with a sebaceous lesion of the forehead histologic study of which showed simply the structure of hypertrophic sebaceous glands. Since the picture was almost identical with that of rhinophyma (so far as the sebaceous factors were concerned) it at once suggested

3. Pollitzer, S.: A Case of Adenoma Sebaceum, J. Cutan. Dis. **11**:475 (Dec.) 1893.

Fig. 1.—Clinical appearance of the lesion.

Fig. 2.—Section showing the regularity in architecture of the glands which indicated that the lesion was not a true adenoma.

a question as to the validity of the apparently general impression that all such sebaceous nodules of the face are nevic. Could an alternative diagnosis such as true adenoma or adenomatoid hyperplasia be considered? In approaching this study one could not be content with the

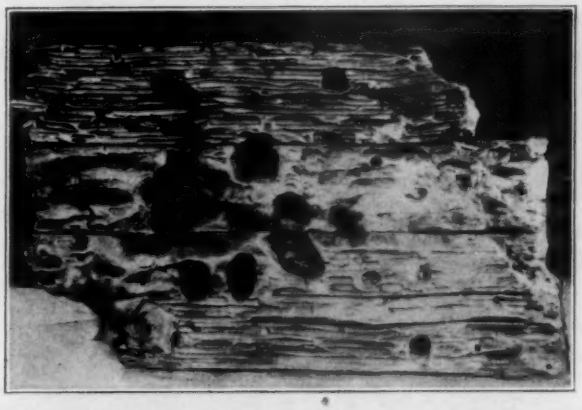

Fig. 3.—Wax reconstruction in the rough; view of the surface of the skin demonstrating the broadened openings of the sebaceous ducts.

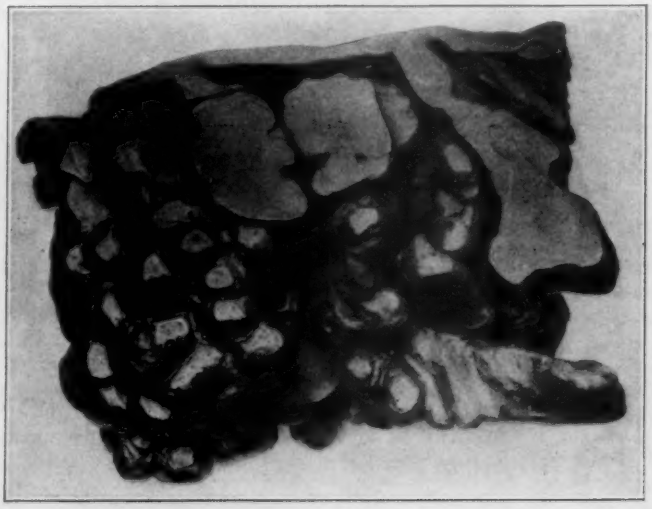

Fig. 4.—Exterior of the wax reconstruction showing the comparatively regular configuration of sebaceous lobules.

routine visual examination of serial sections because it was necessary to determine whether except for complexity the structure of the glands was typically normal or was genuinely adenomatous, i. e., characterized by disordered function and absence of surface connections. Accordingly

a wax reconstruction was resorted to. This showed that surface connections were present. Lobules, while gigantic, were found to be constructed regularly and to communicate with apparently functioning excretory ducts. These ducts in turn emptied widely on the surface of the skin. In brief, the glands were normal except for their complexity, number and size. This at once disposed of the diagnosis of adenoma. Other questions relative to a nevic origin of the lesion will be discussed later.

Fig. 5.—Wax reconstruction cut in two to illustrate the way in which the ducts were exposed for probing into the lobules. The front half of the reconstruction has been turned up (compare with figure 2).

REPORT OF A CASE

The lesion in question was excised from the forehead of a man aged 50, who recalled having had the lesion since he was 18, at which time he had severe acne vulgaris.

A papule in the middle of the forehead just above the level of the eye had been traumatized by occasional squeezing and did not disappear when the acne involuted. When the patient was 40 he presented himself for dermatologic observation. The lesion at that time measured 7 by 3 mm. and showed no evidence of inflammation.

It was not circumscribed and consisted of a group of over twenty minute but well defined pinpoint nodules, some of which were discrete while others were fused with neighboring nodules. When the skin was stretched the lobular outlines became more distinct and the yellowish tint more obvious. It required marked pressure to express the greasy contents of the lesions. There were no comedones. Microscopic examination of expressed material showed that it consisted largely of granular detritus, cholesterol crystals and other lipoidal substances which are to be expected in any old chronic collection of fatty material. Numerous D. folliculorum were consistently observed. The patient was familiar with medical parasitology, and his own observations of the presence of the demodex over a period of years cannot be questioned.

There were no similar lesions elsewhere on the body. The only true nevi observed were two small pigmented moles on the right cheek and one in the left lumbar region.

After excision five years ago there had been no recurrence up to the time of writing.

RECONSTRUCTION TECHNIC

Serial sections 10 microns thick were cut through the entire specimen. Only the central 2 mm. of the lesion was employed for wax reconstruction, as this part exhibited the highest grade of sebaceous proliferation.

The sections, enlarged 100 diameters, were projected onto paper by the Edinger apparatus, and the drawings were made sufficiently large to include the epiderm and the glands which discharged on its surface. Sixty drawings were sufficient to include over a dozen gland complexes indicated in the illustration. Tracings of the outlines of the glands were made from the drawings onto sheets of wax 2 mm. thick; then the wax impressions of the cutaneous structures were cut out and mounted serially. The finished reconstruction was divided into three sections to permit study at different levels.

COMMENT

Since the reconstruction demonstrated that the condition was not a true adenoma, the remaining considerations center around the question whether or not it was congenital, i. e., whether it was a nevus or an adenomatoid hyperplasia. There is no evidence in the history that the lesion was present at birth or that the skin in general was liable to nevic processes. The parents of this patient even up to the age of 75 showed no sebaceous nevi. It would be a simple solution to assume that there might have been a congenital anlage which had remained quiescent up to the patient's eighteenth year, or when the lesion was first observed, but this would be a pure assumption, such as may have been made in some of the other previously described instances of sebaceous nevi. On the other hand, the observations could readily bespeak a simple adenomatoid hyperplasia, particularly in view of what has already been established in general pathology concerning the (generally polypoid) adenomatoid hyperplasias of the glands of the nasal mucosa, stomach, intestines and other structures. It is thoroughly established that in the presence of mild but prolonged stimuli highly exaggerated

hyperplasias of such structures may take place. Provided the stimulus is of a sufficiently low grade there need not be any notable inflammatory reaction even on histologic examination.

An additional and significant point in this connection is the fact that D. folliculorum was present consistently and in large numbers in the lesion. Parasites such as that organism simply by their sluggish movements when these are continued over a long time supply the conditions favorable to the development of any adenomatoid hyperplasia—a pertinent example is schistosomiasis of the rectum. My patient had a highly sebaceous skin; he had had acne vulgaris, which favors the presence of demodex, since the age of 18; hence for about thirty years the stimulus could have been operating. In brief, the conditions for inducing a hyperplasia were at hand.

A survey was made both of cases in which necropsy had been made at the Philadelphia General Hospital and of cases observed in private practice and at the dispensary. In addition, recourse was made to the file of reports on biopsies of the laboratory. It was surprising indeed to find how few disorders conformed to the general scope of benign sebaceous lesions. Only three additional cases were found, while in several others in which the condition had been diagnosed clinically as sebaceous nevi or adenoma it proved to be carcinoma.

The three additional cases occurred in patients aged 50, 68 and 74, respectively. Complete histories were not available. All the lesions appeared on the upper portion of the face near the nose and forehead, and in all the pathologic picture conformed to that just described. Demodex was present in large numbers in all instances. In one case the diagnosis had been made at necropsy. In the other two the disorder had been diagnosed clinically as lupus erythematosus and as basal cell carcinoma, respectively; this accounted for the fact that tissue had been available for biopsy. In other cases not included the disorder was diagnosed clinically as adenoma but on histologic study was found to be a bona fide nevus. My experience in collecting such a limited number of examples of sebaceous hyperplasia leads me to doubt the reported frequency of this type of lesion.

SYNONYMY

In the light of the foregoing comment it is in order to reexamine previously reported cases of disorders falling in this general class of sebaceous hypertrophies, and as a result a number of cases have been found in which the condition appears to be the same as that under consideration. Thus, as a variant sebaceous adenoma Casparry [4] described

4. Casparry, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12.

a type histologically compatible with the disorder in the cases reviewed here, although more widely distributed clinically. Winkler classified this lesion as "type Casparry of the sebaceous adenomas" and characterized it as consisting almost entirely of normally constructed sebaceous glands.

Hirschfeld [5] differentiated certain senile or presenile hyperplastic sebaceous tumors from the general group of sebaceous nevi and described them as follows:

> . . . pinhead sized to pea sized, varying in color, elevated but superficial with minute surface openings from which sebum may be expressed; usually multiple and occurring on the forehead and to a lesser extent on the cheeks and nose; slow growing and occurring after the age of 40.

Reitmann expressed the belief that these lesions are not nevic but are due to a functional hypertrophy of the sebaceous glands and are of the same order as senile angioma and senile pigmentary changes. The consensus among the German observers is that these lesions may serve as points of origin of true neoplasms, particularly of benign cystic epithelioma.

As senile sebaceous gland nevi McCarthy [6] mentioned a fourth division of his classifications of sebaceous adenoma. He described the lesions as appearing on the foreheads or cheeks of old men. He raised the question whether they are true nevi or the result of a pure functional hypertrophy. However, he neither described nor illustrated their histologic picture. The clinical picture, i. e., the location and the age of the patient, suggested a pure hypertrophic process rather than a nevus. It seems that if one were to ascribe the term nevus to a lesion, the point or burden of proof would lie with the proponent.

More recently Nomland [7] reported five cases of a condition which he termed senile sebaceous adenoma. The condition and descriptions in his cases seem to conform closely to the observations in the cases embodied in this report. He summarized his observations by saying that the lesions are quite common in persons with seborrhoea oleosa or acne rosacea and that the lesions are yellow, flat, irregularly rounded umbilicated papules located unsymmetrically on the forehead and in some cases on the face of a patient past the age of 40 (the patients were aged from 45 to 60 in his series). However, the advisability of his inclusion of the term adenoma in his suggested name for this con-

5. Hirschfeld, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12.

6. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931.

7. Nomland, R.: Senile Sebaceous Adenoma, Arch. Dermat. & Syph. **22**: 1004 (Dec.) 1930.

dition appears controversial. Stuart Way [8] in a subsequent paper on the sebaceous glands made an apt point in his critique on the genesis of such lesions. He pointed out that it is reasonable to assume that hypertrophy of preexisting glands plays the major rôle in their production and that hypertrophy of the individual cell as well as that of the gland must be considered.

CONCLUSION

It appears that all the aforementioned types of lesions, although variously named, are identical with the condition considered in this communication. On the basis of the criteria outlined earlier in this paper, none appears to qualify as a true nevus and none appears to be true adenoma. All may be readily classified as functional hyperplasia. For the entire group, and in conformity with the already established tenets of general pathology, the term adenomatoid sebaceous hyperplasia is suggested. This would dispose of the confusion attendant on the loose use of the term nevus but at the same time denote the similarity to the architecture of adenoma while retaining the emphasis on hyperplasia, the real pathologic process concerned.

ABSTRACT OF DISCUSSION

Dr. Fred D. Weidman, Philadelphia: I feel that the practical point about this disorder is that in the past dermatologists have jumped too promptly to the conclusion that these yellowish lesions on the face are nevic, largely because it is known that there exists such a yellow lesion on the face which is really nevic. One should no longer feel that there is only one kind of yellow sebaceous lesion occurring on the face, as has been brought out by Dr. Gilman. He has demonstrated that there is nothing disorderly about the arrangement of the glands; therefore adenoma may be excluded from consideration. There is nothing abnormal about this lesion except its size. It is due merely to hyperplasia. In short, in addition to the true adenomas and to the nevi there is a lesion which may be clinically indistinguishable from these disorders but which may be, at least theoretically, due to pathologic processes other than those causing adenoma and nevi and too numerous to mention. In other words, a simple hyperplasia may be responsible for certain yellow lesions which occur on the face.

As to the rôle of Demodex, that is just as debatable in cases of this disorder as in those of rosacea or other conditions. However, the organism was present at all times over a period of years, and this observation fits in closely with the pathogenesis of analogous lesions in other parts of the body, e. g., adenoid polyposis of the colon, a low grade stimulation of just the kind that is likely to be induced by folliculorum, being present.

Dr. Robert L. Gilman: I was impressed greatly in the study of these cases with the paucity of examples available for complete investigation and with the notable preponderance of the parasites seen on histologic study.

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8. Way, S. C.: The Sebaceous Glands, Arch. Dermat. & Syph. **24**:353 (Sept.) 1931.

CARCINOMA OF THE BREAST WITH PECULIAR CUTANEOUS METASTASES

REPORT OF A CASE

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AND
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ST. PAUL

Cancer originating in the skin and its appendages has received due attention in dermatologic literature, and the pertinent facts are well known. A type of cutaneous cancer which has received scant mention is the metastatic form, in cases of which metastases from tumors in other organs result from circulating emboli or contiguous implantation from lesions which are directly under the integument. In this communication we shall describe a rare example of extension into, and involvement of, the skin from a mammary cancer.

The skin may be involved by mere extension of underlying cancer, and ulceration and papillary tumors may result; such lesions are usually easily recognized. Another common type of carcinomatous metastasis results in a single or in multiple lenticular nodes occurring in or on the skin and may offer considerable difficulty in diagnosis unless a biopsy is made.

Carcinoma of the breast is the condition which most commonly results in cutaneous metastases. Next in order are primary tumor of the gastro-intestinal tract, tumor of the female reproductive system and hypernephroma.

It is easy to understand the development of cutaneous lesions in cancer of the breast. They may result from local persistence of malignant tissue after excision of the primary tumor mass, and involvement of the regional nodes is common and may obstruct lymph drainage, thus allowing malignant cells which might otherwise be carried through the body to persist and grow, a local cutaneous lesion resulting. The scar tissue resulting from extensive surgical dissections may act in a similar manner as an obstruction to lymph drainage, and any tumor cells left or implanted in the field at the time of operation may continue to grow.

From the Division of Dermatology, University of Minnesota Medical School, Dr. H. E. Michelson, Director.

Read at the Fifty-Ninth Annual Meeting of the American Dermatological Association, Inc., Swampscott, Mass., June 5, 1936.

Several recent reports [1] have suggested that metastases are particularly prone to appear in areas treated by irradiation, a therapeutic procedure commonly employed after surgical excision of carcinoma of the breast.

Carcinoma of the breast may lead to many different cutaneous manifestations. Necrosis of the tumor not infrequently leads to ulceration because of the superficial nature of the primary lesion, while proliferation of the tumor tissue may produce papillary or fungating growth. In addition to this involvement by direct extension, cancer cells may be carried into the skin by way of the blood and lymph streams, resulting in general or local metastases. Such metastatic lesions may appear as multiple firm papules or lenticular nodes or as more diffuse bands or plaques. These diffuse lesions develop by coalescence of smaller papules or by continuous extension from a single focus. Cystic or vesicular forms are not common, although Matras [2] in classifying the cutaneous lesions secondary to carcinoma of the breast mentioned Riehl's description of such lesions which later develop into nodes.

The diffuse infiltration of the thoracic wall after carcinoma of the breast may be early and rapid or delayed in its course, but usually there results an extensive boardlike involvement. If the process takes place slowly, a constricting band may result, known as cancer en cuirasse. If the infiltration takes place rapidly the skin becomes reddened and edematous; the border of the eruption is elevated, and general toxic symptoms may appear; the clinical course may resemble that of erysipelas, and as a rule the patient soon dies.

Although carcinomatous extension simulating erysipelas is not uncommon, American dermatologists have written little about it. The resemblance to erysipelas was mentioned by Unna, and the condition was later described by Küttner [3] as erysipelas carcinomatosum. It may be differentiated from cancer en cuirasse by the more chronic course and the absence of fever and of the scleroderma-like induration which is present in cancer en cuirasse. Rüder,[4] in 1928, pointed out that the manner of extension of erysipelas carcinomatosum differs from that observed in Paget's disease by being subepidermal rather than intraepidermal and that it differs from the usual extension of adenocarci-

1. Schürch, O.: A Case of Cutaneous Metastasis in the Field of Irradiation of Pyloric Carcinoma, Ztschr. f. Krebsforsch. **41**:47, 1934. Marschall, F. H.: Ueber karzinomatöse Hautmetastasen im Röntgensbestrahlungsfeld bei Lippen- und Drüsenkrebs, Dermat. Wchnschr. **100**:137, 1935.

2. Matras, A.: Das sekundäre Karzinom der Haut, Wien. klin. Wchnschr. **44**:1408, 1931.

3. Küttner, H.: Beiträge zur Pathologie des Mammacarcinoms, Beitr. z. klin. Chir. **131**:1, 1924.

4. Rüder, F. B.: Zur Frage des Erysipelas carcinomatosum bzw. subepidermoidalen Karzinomas der Mamma, Zentralbl. f. Gynäk. **52**:236, 1928.

noma in that it propagates by direct growth in the blood vessels rather than by cells being carried in the blood stream. Some of the other observers expressed the belief that the infiltration extends through the lymphatics rather than through the blood vessels.

Many typical examples of erysipeloid carcinoma have been described. Some of the atypical manifestations are deserving of greater attention because they have simulated other diseases, thus offering great diagnostic difficulties.

Barber,[5] in 1931, presented before the Royal Society of Medicine a patient with Paget's disease which had shown extensive surface growth. In the histologic sections masses of malignant epidermal cells were present within the lumens of the blood vessels.

In the same year Rasch[6] described a case of carcinoma of the breast which involved the skin in a manner only slightly resembling erysipelas. The surface of the skin was smooth except for an area over the sternum where small yellow raised translucent cysts were present. He regarded the disorder as erysipelas carcinomatosum (Küttner) but proposed the name carcinoma erysipelatodes acutum because of the undoubted presence of carcinoma and the absence of true erysipelas. He distinguished the condition from cancer en cuirasse by the absence of scleroderma-like changes and by its extension through the blood vessels rather than by way of the lymph vessels and tissue spaces, and he emphasized the acuity of the process.

In 1933 F. Parkes Weber[7] applied the name carcinoma telangiectaticum to a carcinoma of the breast which at the time of operation showed minimal cutaneous changes, which later became extensive and consisted of diffuse redness with slightly raised areas of individual dilated blood vessels without purpura but with some hyperpigmentation and a smooth glossiness which quite obscured the true nature of the change. In this case there was no resemblance to erysipelas.

In the same number of the *British Journal of Dermatology* Van Vonno[8] presented a photograph of a similar disorder with a like histologic picture.

Nix,[9] in 1933, described a case of carcinoma of the breast accompanied by extensive reddish brown cutaneous induration with deep and

5. Barber, H. W.: Paget's Disease of the Nipple Associated with Diffuse Carcinomatosis of the Chest Wall, Proc. Roy. Soc. Med. **25**:670, 1932.

6. Rasch, C.: Carcinoma Erysipelatodes, Brit. J. Dermat. **43**:351, 1931.

7. Weber, F. Parkes: Bilateral Thoracic Zosteroid Spreading Marginate Telangiectasia, Brit. J. Dermat. **45**:418, 1933.

8. Van Vonno, N. C.: A Case of Carcinoma Telangiectaticum, Brit. J. Dermat. **45**:423, 1933.

9. Nix, W.: Ueber karzinomatöse Hautmetastasen unter dem Bilde eines Hämolymphangiomas, Dermat. Wchnschr. **97**:1551, 1933.

superficial blue ridges resembling small thrombosed blood vessels. There were numerous firm cystic lesions resembling vesicles, but they contained no fluid. The microscopic sections showed that the ridges were blood vessels filled with solid masses of carcinomatous epithelial cells, and the cystic appearance was due to necrosis in the center of similar cellular masses in the lymph vessels.

The clinical resemblance of such disorders to Paget's disease is well exemplified in the case described by Nanta and Salvador,[10] in which the cutaneous lesions developed near the nipple early in the course of the disease. The edematous erythematous infiltration spread peripherally, leaving a residual vascular dilatation. Two zones of involvement were described: (1) solid elevated edematous plaques with areas of ecchymosis and (2) a zone of angiomatous dilatation. Areas in the second zone frequently presented an advancing elevated border like that of the plaques. The cystic elevations on the surface of the skin were punctured to determine the contents: first red and then darker blood escaped. In the angiomatous zone the capillaries contained cords of epithelial cells. The authors thought that this invasion resulted in vascular obstruction which led to the angiomatous appearance. The lymph vessels remained uninvolved.

REPORT OF CASE

Mrs. F. P. was 38 years old at the time she noted a painless massive diffuse enlargement of the right breast (fig. 1). Both breasts were removed in August 1933, the right because of its size and the left because of a possibility that "it might enlarge later." The patient was told no cancer was present, and the axillary nodes were not dissected. In 1934 there developed painless progressive edema of the right hand and a cutaneous eruption on the neck and chest which later involved the anterior and lateral surfaces of the chest and extended down the right arm. There were occasional periods of itching.

On examination indurated edema of the right hand and arm was noted. The cervical and axillary lymph nodes were not palpable. There were redness and diffuse thickening of the skin of the anterior and lateral surfaces of the chest and upper portion of the abdomen, with firm elevated striae and scattered nodules. There were also many lesions having the appearance of vesicles. These were firm walled, and when they were opened practically no fluid could be expressed.

COMMENT

The microscopic changes are shown in figures 2 and 3. The malignant epithelial areas were sharply circumscribed, showing no involvement of the cutaneous epithelium or of any other tissues in the skin except the small vessels. The masses of malignant cells were easily recognized as adenocarcinomatous. Many of them were so superficially

10. Nanta, A., and Salvador: Angio-épithéliomatose cutanée, Bull. Soc. franç. de dermat. et syph. **42**:653, 1935.

Fig. 1.—Telangiectatic and cystic lesions superimposed on a diffusely infiltrated skin, representing an unusual form of cutaneous eruption following carcinoma of the breast.

Fig. 2.—Adenocarcinomatous epithelium encysted in dilated blood vessels. Such intravascular growth of malignant tissue is characteristic of subepidermoid carcinoma of the breast.

situated that the surface of the skin was elevated, resulting in papular lesions; the central areas of necrosis in some of these papules produced the clinical impression of small cysts or vesicles.

Although the malignant epithelial cells filled the entire lumen of most of the vessels there was no evidence of direct attachment to, or involvement of, the vascular endothelium. The site of penetration from the original tumor into the vessels was not apparent in the sections studied.

The vascular structure was simple, consisting of a single layer of endothelium, and showed no structural features which allowed recog-

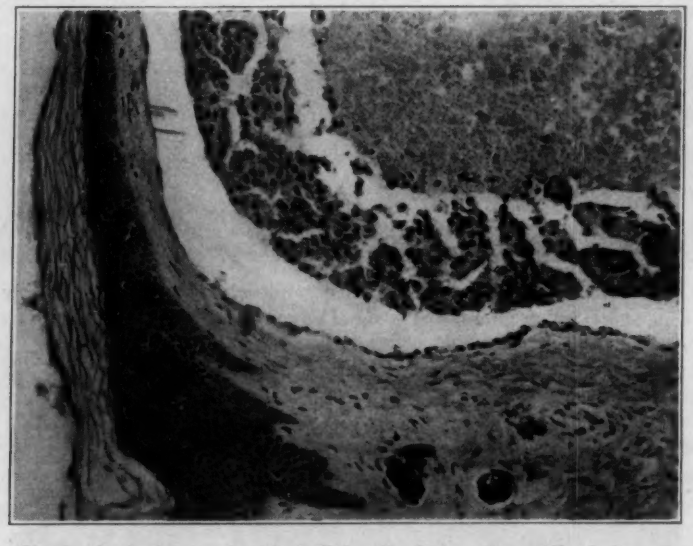

Fig. 3.—A single layer of endothelial cells forms the wall of the cyst. The malignant tissue grows within the lumen and is not attached to the wall.

nition of its nature. The presence of red blood cells in some of the areas of central necrosis suggested that at least some of the vessels were blood vessels rather than lymphatics.

The term comedo-adenoma of the female breast was used by Bloodgood[11] to describe a "basal cell tumor apparently arising in ducts"; other authors spoke of this condition as intraductal carcinoma. The reason for Bloodgood's use of the word comedo lies in the appearance of the freshly cut surface of the tumor and has nothing to do with the visible clinical manifestations of the disease, which resembles other

11. Bloodgood, J. C.: Comedo-Carcinoma (or Comedo-Adenoma) of the Female Breast, Am. J. Cancer **22**:842, 1934.

tumors of the breast and may be benign or malignant depending on whether it is or is not associated with areas of true adeno-carcinoma. The microscopic structure is that of adenomatous epithelial growth within the ducts of the tissues of the breast, and there is a surprising resemblance to the endothelioma (basal cell cylindroma) of the scalp so thoroughly studied by Friboes. In the absence of any adeno-carcinomatous change comedo-adenoma is a benign tumor of the breast which shows some tendency to recur.

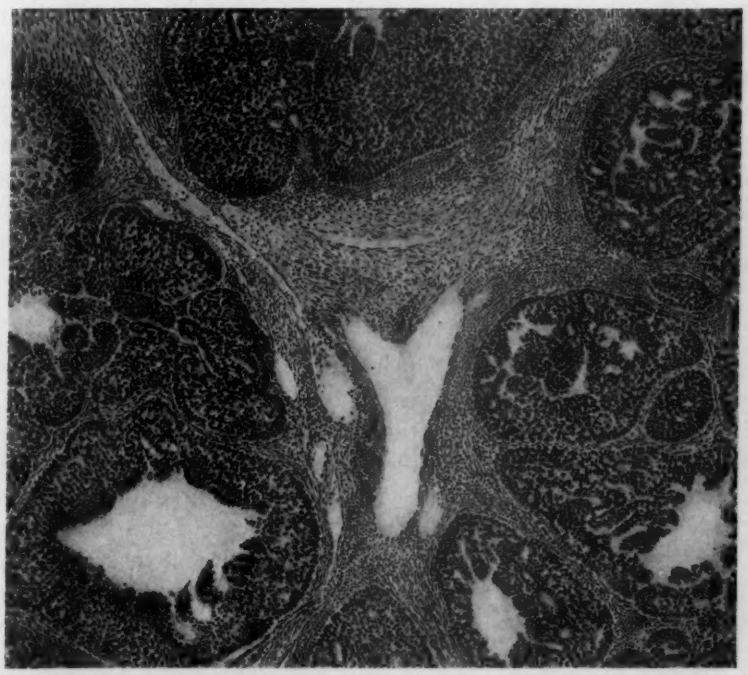

Fig. 4.—This reproduction of one of Bloodgood's [11] photomicrographs shows the superficial resemblance to subepidermoid carcinoma, namely, sharply circumscribed masses of tumor cells with numerous areas of central necrosis. A columnar basal layer of epithelium forms the outer wall and distinguishes comedo-adenoma from subepidermoid carcinoma of the breast.

Microscopically the disorder in this case showed a superficial resemblance to Bloodgood's comedo-adenoma in that sharply circumscribed masses of epithelial carcinoma with central areas of necrosis (fig. 4) were present. In our case there was in the cellular mass a tendency to the development of cell strands, and the growth could be regarded as adenocarcinoma, but the cells were not firmly attached to the surrounding membrane which consisted of a single thickness of flat endo-

thelial cells. The lesions could be differentiated by examination of the border of the mass of malignant cells.

In Bloodgood's comedo-adenoma the outer layer consists of a basal columnar epithelium which is the basal layer of the epithelial duct system of the breast tissue.

There seems to be no way to differentiate erysipeloid carcinoma in its simplest form from the eruption observed in our patient. In both the outstanding feature is the extension of the epithelial carcinoma by way of the smaller vessels. The difference in the clinical appearance depends largely on the depth of the involved vessels.

The presence of red blood cells in some of the central necrotic areas is proof that the carcinoma spreads through blood vessels. However, the structure of the vessels in our case was a single layer of endothelium, and it is impossible to state whether the extension was limited to blood vessels or whether lymphatic vessels were also involved.

Histologically the differentiation of Paget's disease from these other conditions is simple. Characteristic Paget cells and the typical intra-epidermal proliferation are absent in the conditions referred to in this study.

Schreiner and Volavsek [12] have recently described an extensive carcinomatosis of the skin in a man, the involvement resulting from a cancer of the breast which was overlooked in the early stages of the disease. They expressed the belief that the carcinoma first involved the large lymphatic vessels of the thorax and then extended in a retrograde manner, producing edema of the lower extremities followed by diffuse cutaneous induration. This involvement of the skin extended up the legs and finally involved nearly the entire surface of the body. The surface was smooth and glossy, and the skin was taut and extremely hard. There were areas of hyperpigmentation but no redness or other features resembling erysipeloid carcinoma. Schreiner and Volavsek regarded the disorder as a rare example of *carcine éburnée* of Alibert. The histologic sections were of interest because they showed no dilated small vessels filled with cancer cells but rather a uniform sheet of carcinoma cells parallel with the epidermis at the level of the lymphatic vessels in the middle portion of the cutis.

SUMMARY

The interest in this case of carcinoma of the breast lies in the unusual cutaneous involvement which had the appearance of a vesicular eruption and which was accompanied by a moderately severe pruri-

12. Schriener, K., and Volavsek, W.: Ueber das Carcine eburnée Aliberts, Arch. f. Dermat. u. Syph. **174**:22, 1936.

tus. The microscopic picture provided a good demonstration of the intravascular manner of extension with masses of carcinoma cells surrounded by vascular endothelium. There was central necrosis of many of these cellular masses, leading to the development of small cystic lesions resembling vesicles. In some areas in which the necrosis had not advanced to liquefaction there was a superficial resemblance to the picture of comedo-adenoma of the breast as described by Bloodgood.

In such an eruption one must consider the following diagnostic possibilities:

1. Paget's disease. This appears in the region of the nipple and resembles a dermatitis with exudation, scaling, crusting, hyperpigmentation and finally induration. There is no telangiectasia at any stage.

2. Lympho-hemangioma. This is a nevus which seldom has its onset so late in life as the disorder in our case. The eruption consists of dilated blood and lymph vessels with elevation of the capillary loops, resulting in small cystic lesions in the skin. There is no induration of the tissues, and the border shows no elevation or active spreading.

It seems that the term erysipeloid carcinoma is applied to many eruptions which do not reproduce the characteristics of that disorder. Only when redness, elevation and active spreading at the border are present does the term apply. Not infrequently a single area of cutaneous extension from carcinoma of the breast takes on such an appearance, but seldom is the entire eruption of that nature.

In the case reported here, as well as in the cases of Parkes Weber, Van Vonno, Nix and Nanta and Salvador, there were features resembling hemangioma or hemolymphangioma superimposed on a background with some of the characteristics of erysipeloid carcinoma. In the presence of such features and in the absence of an acute febrile clinical course we question whether one should refer to the disorder as carcinoma erysipelatodes. The term subepidermoid carcinoma of the breast may be used to include all disorders in which the diffuse cutaneous infiltration is an outstanding feature.[13]

CONCLUSIONS

A case of cancer of the breast with local cutaneous metastases is reported.

The appearance of the skin was that of a diffuse cystic inflammation and quite belied the underlying cause.

Cystic cutaneous extension from cancer of the breast is due to actual cancer cells encysted in endothelium-lined vessels.

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13. Fischer, H.: Das subepidermoidale Mammakarzinom, München. med. Wchnschr. **78**:497, 1931. Rüder.[4]

ABSTRACT OF DISCUSSION

Dr. J. Frank Fraser, New York: The sections indicate metastases by vascular embolism. The usual route of extension of carcinoma of the breast to the skin is by the lymphatics; viz., cancer cells travel downward with the lymph stream (lymphatic embolism) until they reach the deep fascia and muscular aponeurosis. There they meet resistance, and their course is changed. Some travel along the muscle plane; then they grow upward by lymphatic infiltration, following the walls of the lymph channels against the stream, producing cancer nodules in the skin (lenticular carcinoma). This is the "permeation" of Handley.

In regard to the authors' reference to Paget's disease as an infiltrating carcinoma, I think the balance of histologic evidence today favors the view that Paget's disease is a duct carcinoma. If the duct carcinoma does not involve the epidermal terminations of the milk ducts, the picture of Paget's disease does not develop. In Paget's disease metastases occur by cancer cells breaking through the duct walls and infiltrating the tissues of the breast.

Dr. David L. Satenstein, New York: I have a number of specimens in which both types of metastatic deposits can be seen. After the complete ablation of the breast, in the scar tissue a radiating lymphangitis extends from the scar tissue in all directions, and the lymph vessels are observed to be full of large cells, the picture being similar to that in the sections presented by Dr. Freeman and Dr. Lynch. There are also alongside of them capillaries filled with the same type of cells which may be recognized as capillaries by the fact that they contain a considerable number of blood cells as well as pathologic cells. This picture does not uncommonly follow complete ablation of the breast. I have not seen metastases radiate up, but I have seen them radiate into the arm and down to the abdomen. Eller reported a case of such involvement, and my co-workers and I have some beautiful specimens illustrating all these features.

PSEUDOXANTHOMA ELASTICUM

PROOF OF CALCIFICATION OF ELASTIC TISSUE; OCCURRENCE WITH AND WITHOUT ANGIOID STREAKS OF THE RETINA

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It has long been our observation that the degenerated elastic tissue in areas of pseudoxanthoma elasticum when stained with hematoxylin and eosin assumes a blue or blue-red color similar to that of calcium deposits in other pathologic conditions. In this paper it is not our intention to speculate on the reasons for our observations or to include suggested similar observations in other dermatoses. However, in general pathology the tendency for calcium to infiltrate degenerated elastic tissue is well recognized. Since this study was completed we have learned in the literature of a similar observation made previously. Friedmann [1] reported a case of typical pseudoxanthoma elasticum occurring in a woman aged 25, in which he demonstrated the presence of calcium deposits in the involved elastic tissue by microscopic means. Gans [2] stated that only one other case of pseudoxanthoma elasticum with calcification had been reported, and that the diagnosis was questionable, the changes being observed in a man aged 74 who also had senile elastosis.

The literature on pseudoxanthoma elasticum has been repeatedly summarized. Many of the recent papers deal with the association of pseudoxanthoma elasticum and angioid streaks, but Montgomery and Benedict,[3] in a complete paper published recently emphasized the fact

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Read at the Fifty-Ninth Annual Meeting of the American Dermatological Association, Inc., Swampscott, Mass., June 5, 1936.

1. Friedmann, Martin: Ein Beitrag zur Kenntnis des Pseudoxanthoma elasticum (Darier), Arch. f. Dermat. u. Syph. **134**:151, 1921.

2. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1927, vol. 1, p. 109.

3. Benedict, W. L., and Montgomery, H.: Am. J. Ophth. **18**:205 (March) 1935.

that both pseudoxanthoma elasticum and angioid streaks may occur independently, though association is probably the rule. Our cases confirm their opinions.

The following three cases illustrate the three possibilities, namely, pseudoxanthoma elasticum with angioid streaks, pseudoxanthoma elasticum alone and angioid streaks alone.

REPORT OF CASES

CASE 1.[4]—*Pseudoxanthoma elasticum with associated angioid streaks of the retina and chorioretinitis.*

A German woman aged 40 presented a cutaneous eruption of about thirty years' duration. She stated that she had suffered from progressive loss of vision for about two years.

The eruption (fig. 1) when first noted consisted of small yellowish areas on the left side of the base of the neck, which appeared when the patient was about 9 years old and had gradually increased. When the patient was 30 similar lesions were noted in the groins, and later lesions developed in the axillae.

Examination showed that the eruption was most marked at the base of the neck, appearing as a band of irregular width (10 cm. or more) extending around the neck. It consisted of a reteform papular chamois-yellow discoloration. In one area there was definite formation of papules which were from 2 to 3 mm. in diameter. Similar lesions were observed in the groins, along the entire length of the inguinal fold, and in both axillae. In the reteform areas the normal surface architecture of the skin was retained. Similar lesions were present on the buccal mucosa.

The calcium content of the blood was 13 mg. per hundred cubic centimeters of serum.

The essential ocular findings were reported by Dr. Klien to be as follows: Vision was 4/10 in the right and 1/10 in the left eye. The eyes were normal externally, and the media were clear. Ophthalmoscopic examination of the right fundus showed a number of angioid streaks in a semicircular arrangement around the disk with radial projections toward the periphery in several places. The left fundus showed more involvement, with angioid streaks and also hemorrhages, choroidal atrophy and pigmentation.

CASE 2.[5]—*Pseudoxanthoma elasticum without angioid streaks.*

An American woman aged 56 stated that her cutaneous trouble was of from four to five years' duration. She suffered from occasional slight soreness about the umbilicus.

Examination revealed an eruption in the vicinity of the umbilical, inguinal (fig. 2), popliteal and axillary regions. It consisted of a chamois-colored reticulation of the skin, with no elevation or papule formation except in a restricted area about the umbilicus. There were no angioid streaks of the retina or other

4. Nomland, R., and Klien, B.: Pseudoxanthoma Elasticum of the Skin, Arch. Dermat. & Syph. **27**:849 (May) 1933.

5. Nomland, R., and Scull, R. H.: Pseudoxanthoma Elasticum, Arch. Dermat. & Syph. **33**:929 (May) 1936.

Fig. 1 (case 1).—Photograph showing the character of the eruption about the neck.

Fig. 2 (case 2).—Photograph showing the character of the lesions of the inguinal regions and the associated striae distensae.

abnormalities, but vision was rather poor. The general history and results of medical examination were otherwise essentially irrelevant.

The calcium content of the blood was 11.2 mg. per hundred cubic centimeters of serum.

CASE 3.—*Angioid streaks without pseudoxanthoma elasticum.*

A man aged 56 was seen in the ophthalmologic clinic because a cilia was scratching his eyeball.

Vision was 0.4 plus in the right and 0.6 minus in the left eye, being corrected to about normal with appropriate lenses. Added correction was necessary for reading.

There were typical angioid streaks around both disks, with radial extension to the periphery. Neither macula showed gross lesions, but the entire region of the posterior pole of each had a finely granular appearance. There were slight contraction of the fields and slight increase in the size of the blindspot.

On thorough examination of the skin no pseudoxanthoma elasticum was found. Senile keratoses, freckles on the backs of the hands and a keratosis on the lobe of the left ear were the only cutaneous abnormalities.

HISTOLOGIC AND CHEMICAL STUDY

The histologic changes are shown in figures 3, 4, 5, 6, 7 and 8.

Several biopsies were made in cases 1 and 2. The tissues, fixed in 50 per cent alcohol and blocked in paraffin, were stained with hematoxylin and eosin, acid orcein, Weigert's elastic tissue stain and von Kossa's silver impregnation stain. In both cases there were present in the subpapillary layer and the middle portion of the cutis diffuse and circumscribed areas of elastic fibers occurring as large coils which were thickened, broken and fragmented. They assumed a decidedly darker color with all elastic tissue stains than does normal elastic tissue. The degenerated thickened fibrils took an intense blue stain with hematoxylin and turned dark brown to black with von Kossa's silver stain. This appeared to be an indication, though not an absolute proof, that calcium was deposited in or in and about the degenerated elastica. There was no inflammatory reaction or evident atrophy of the epidermis.

On incineration of unstained sections, the structure of the degenerated fibers was still clearcut, but only faint outlines of the tissue elsewhere were discernable. This remaining heavy mineral débris was proved by the following method to be calcium in the form of the phosphate.

Unstained sections were mounted in 40 per cent alcohol, and a few drops of 3 per cent sulfuric acid were allowed to run in under the cover glass according to the method described by Schmorl.[6] Within a few minutes one could see with the high dry power of the microscope the areas of degenerated elastic tissue replaced by crystals of calcium sulfate (gypsum), formed from the action of sulfuric acid on the calcium phosphate in the tissue. It was then demonstrated that there was no calcium in the tissue in the form of carbonate by adding dilute hydrochloric acid to an unstained section mounted in water. These specimens were observed microscopically for over an hour, and no bubbles of carbon dioxide were observed.

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6. Schmorl, G.: Die pathologisch-histologischen Untersuchungsmethoden, ed. 12 and 13, Leipzig, F. C. W. Vogel, 1922, p. 179.

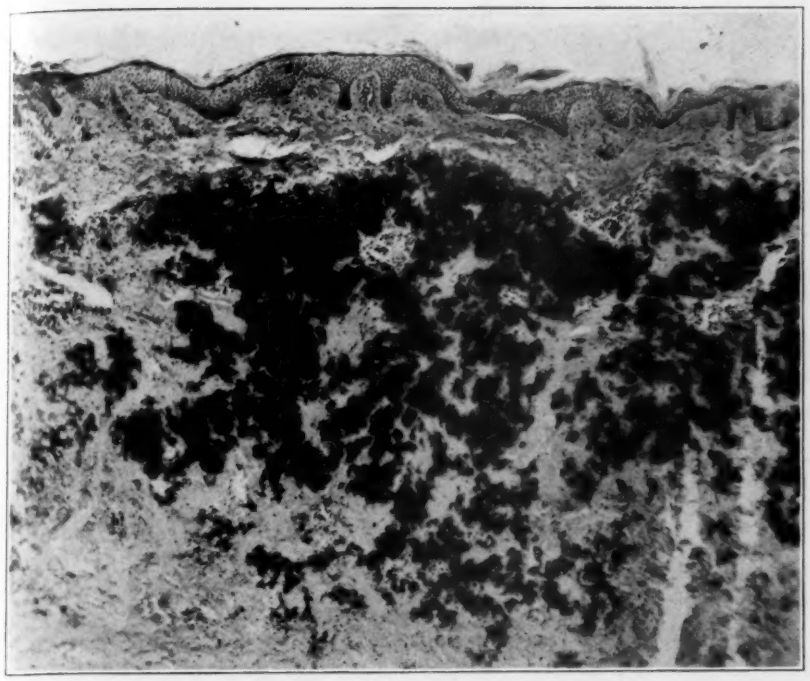

Fig. 3 (case 1).—Photomicrograph showing dark hematoxylin staining of the degenerated and calcium infiltrated elastic tissue with hematoxylin and eosin (× 60).

Fig. 4 (case 2).—Photomicrograph showing the degenerated and calcium infiltrated elastic tissue with Weigert's elastic tissue stain (× 150).

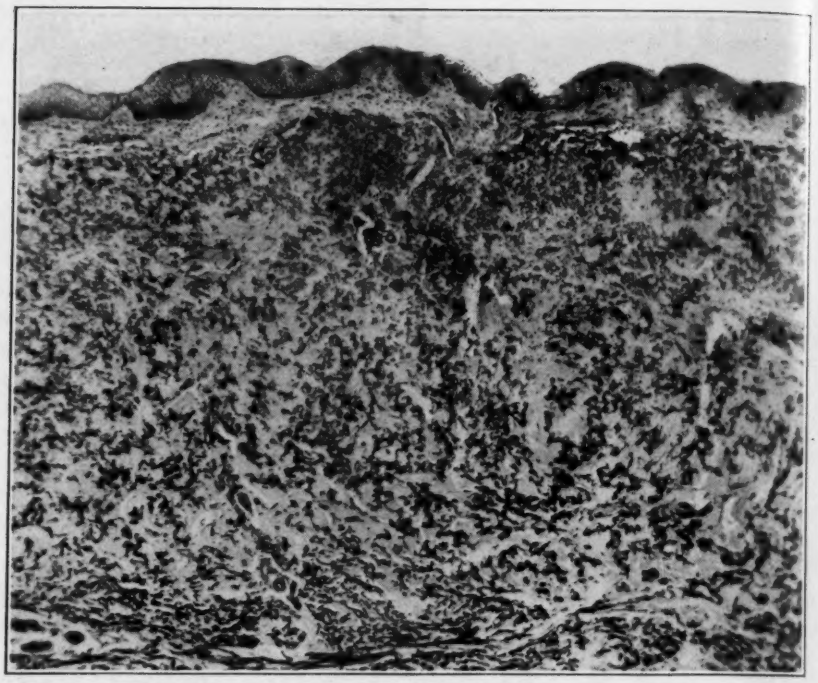

Fig. 5 (case 2).—Photomicrograph showing degenerated and calcium infiltrated elastic tissue stained with acid orcein (× 60).

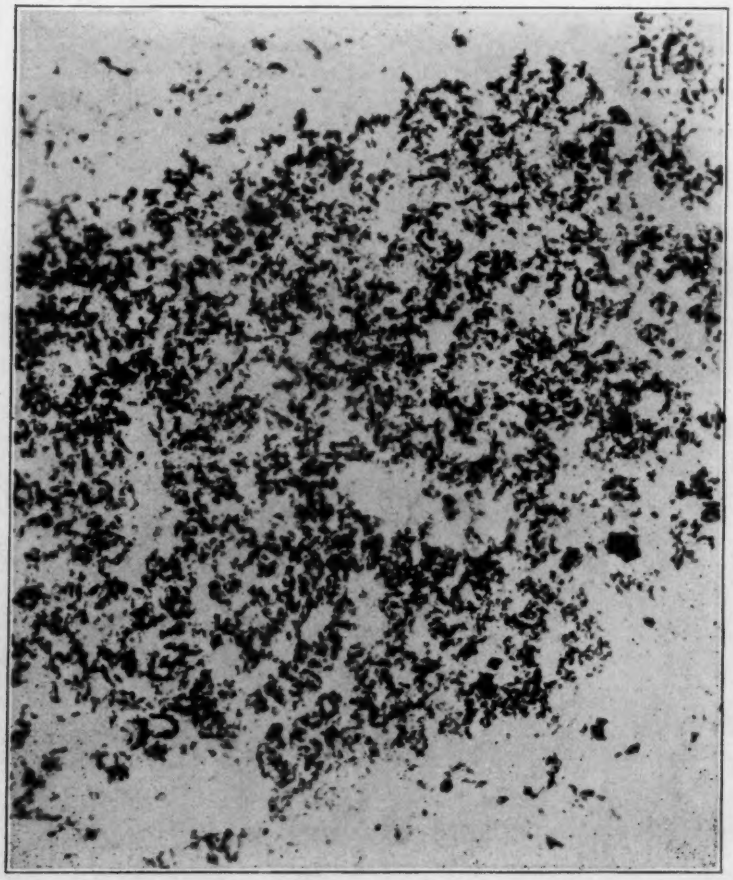

Fig. 6 (case 2).—Photomicrograph showing the mineral débris remaining after incineration. Note the faint outline of the overlying epidermis (× 80).

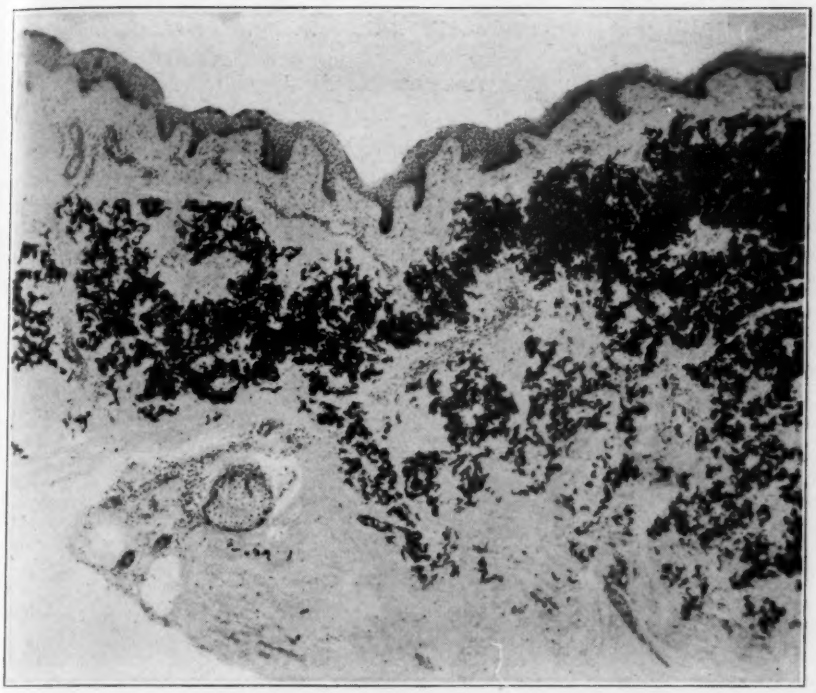

Fig. 7 (case 1).—Photomicrograph showing the dark brown to black staining of the calcium infiltrated elastic tissue with von Kossa's silver impregnation stain for calcium (× 60).

Fig. 8 (case 1).—Photomicrograph made with polarized light showing crystals of calcium sulfate in the tissues formed by the action of dilute sulfuric acid on the calcium phosphate (× 290).

QUANTITATIVE DETERMINATION OF CALCIUM IN THE SKIN

Tissues were examined quantitatively for calcium, material being obtained from one area of pseudoxanthoma elasticum in each of the two cases of the disease, from a noninvolved area in one case of pseudoxanthoma elasticum and from the abdomen in three control cases. The persons used as controls were three women who were of about the same age and weight and had had about the same number of pregnancies as the patients in cases 1 and 2. It was observed that areas of pseudoxanthoma elasticum contained from three or four to many times as much calcium as the skins of persons not having the disease and as the skin of a noninvolved area in a patient who had pseudoxanthoma elasticum elsewhere.

Results of Quantitative Determination of Calcium in Areas of Pseudoxanthoma Elasticum and in "Normal" Skin

Tissue	Weight of Desiccated Skin, Gm.	Weight of Calcium Oxide, Gm.	Percentage of Calcium
Pseudoxanthoma elasticum; involved area (case 1)	0.5217	0.0247	4.730
Pseudoxanthoma elasticum; involved area (case 2)	0.1506	0.0093	6.180
Pseudoxanthoma elasticum; noninvolved area (case 1)	0.8050	0.0012	0.150
Control no. 1	0.0970	0.0015	1.540
Control no. 2	0.8037	0.0008	0.995
Control no. 3	0.4955	0.0005	0.101

COMMENT

Calcification of the degenerated elastic tissue of pseudoxanthoma elasticum should not be an unexpected phenomenon, because calcification of elastic tissue is a common observation in general pathologic conditions. It is rather surprising that, because of the well known tendency of pseudoxanthoma elasticum to take up hematoxylin, which we consider practically as specific a stain for calcium as any, calcium deposition in degenerated elastica has not previously received more intensive study. We could find no figures giving the normal calcium content of the skin (epidermis and cutis) from chemical analysis; so we made analyses on the skin of three normal controls. In areas of pseudoxanthoma elasticum the amount of calcification in the tissue was so many times higher than normal that the increase was unquestionable. The one uninvolved area, analyzed from the first case, showed that the increase was not present there. Microchemical methods, incineration and application of von Kossa's stain confirmed the fact that there was increased calcium deposition. The calcification was shown to be in the form of the phosphate by reactions with sulfuric acid, calcium sulfate (gypsum crystals) being formed in the tissues. Calcium carbonate was not present, as shown by the test with dilute hydrochloric acid.

The morphology of the calcium deposits, as shown by incineration and application of von Kossa's stain, is identical with the morphology of the degenerated elastic tissue stained with acid orcein and with Weigert's elastic tissue stain.

The three cases reported illustrate and confirm the contention of Montgomery and Benedict that pseudoxanthoma elasticum and angioid streaks do not necessarily occur together and that each one can develop independently.

SUMMARY AND CONCLUSIONS

Three cases are herein reported of the three possible combinations of pseudoxanthoma elasticum and angioid streaks of the retina: (1) pseudoxanthoma elasticum and angioid streaks, (2) pseudoxanthoma elasticum alone and (3) angioid streaks alone.

We have demonstrated by staining methods, by incineration, by quantitative chemical analysis and by microchemical means that the degenerated elastic tissue in pseudoxanthoma elasticum is richly infiltrated with calcium and that this calcium occurs in the form of calcium phosphate.

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Dr. Richard H. Jaffé, Director of the Department of Pathology, Cook County Hospital, Chicago, offered helpful suggestions relative to the laboratory technic.

ABSTRACT OF DISCUSSION

Dr. Louis A. Brunsting, Rochester, Minn.: Drs. Finnerud and Nomland are to be congratulated on their concise and constructive work. A few months ago they spoke to me of their observations, and since then my co-workers and I have had opportunity to confirm these observations in one case. A man aged 26 came to the clinic because of epilepsy, and during the routine examination the ophthalmologist detected angioid streaks of the retina and referred the patient to us for examination of the skin. On first inspection there seemed to be no changes in the skin, but in a good light we saw the early changes of pseudoxanthoma elasticum in the anterior axillary folds. A specimen consisting half of involved skin and half of adjacent normal skin was incinerated, and the calcium content was recorded to be 11 mg. per hundred grams in the involved area and 7.2 mg. in the adjacent apparently normal skin.

Early evidence of pseudoxanthoma elasticum may easily be overlooked, and in cases in which the diagnosis is doubtful a microscopic examination of tissue should be made.

Dr. Fred D. Weidman, Philadelphia: There is no doubt that calcium was demonstrated in the form of calcium phosphate in the authors' cases. That calcium was present can be recognized even in sections stained with hemotoxylin and eosin, but magnesium and perhaps also iron salts may be present. The last two salts are much more difficult to demonstrate by ordinary chemical and staining technic, but fortunately Dr. Gaul has developed a microspectroscopic method by which the presence of these salts may be detected.

I note that in Dr. Finnerud's cases the calcareous material was located in the upper parts of the corium. It seems to be the consensus that such material usually occurs in the deeper parts, and this has been cited as a diagnostic point in differentiating pseudoxanthoma elasticum from senile elastosis. I have studied a number

of cases of the latter condition, and in some the elastic tissues occurred deep. Since the location varies in both of those diseases I doubt that it has much value in differential diagnosis in cases of elastic tissue overgrowths.

I agree with Dr. Finnerud that the calcium present in pseudoxanthoma elasticum does not bear any relation to the fundamental pathologic processes of pseudoxanthoma elasticum. It is simply a part of the general pathologic process of calcification that elastic tissue of whatever position and in whatever connection predisposes to calcium deposition. Similarly, lipoids, particularly soaps, predispose to calcium deposits, and it is possible that in the authors' cases staining of material with sudan III would reveal the presence of fat just as it has in cases of senile elastosis (The Pathology of the Yellowing Dermatoses, ARCH. DERMAT. & SYPH. **24**:954 [Dec.] 1931).

From now on dermatologists will be called on to examine the skin most carefully for the early stages of pseudoxanthoma elasticum, as indicated by Dr. Brunsting. Ophthalmologists will call on dermatologists to examine patients with angioid streaks of the retina. Indeed, this occurred in the case of a patient presented before the Philadelphia Dermatological Society. Examination was made in the evening under a rather poor light, and it was difficult indeed to demonstrate the yellow color.

DR. CLARK W. FINNERUD: I think Dr. Brunsting's observations are especially interesting in that he was dealing with a case of early involvement so far as the pseudoxanthomatous lesions were concerned. Why diseased tissue in general often takes up calcium more readily than normal tissue is not well understood. The morphology, as shown in the sections after incineration, was practically identical with the morphology of the clumps of degenerated elastica in the sections stained with acid orcein and Weigert's elastic tissue stain.

Our experience was the same as Dr. Weidman's in one instance. A patient was seen in the ophthalmologic clinic, and a diagnosis of angioid streaks of the retina was made. The physician who observed these streaks thought that the cutaneous changes must be pseudoxanthoma elasticum and brought the patient to our clinic.

I was interested in Dr. Weidman's remarks about the microspectroscopic examination, and I hope that we shall be able to make such examinations. As to senile elastosis, in patients in whom what is thought to be pseudoxanthoma elasticum develops after the age of 50 or 60, we have found it almost impossible to ascertain, clinically at least, where one process ends and the other begins. There is no doubt in our minds but that calcium infiltration is present in senile elastosis and in other diseases in which the fibrous tissues take a bluish stain with hematoxylin and eosin, but we have not yet had an opportunity to study these conditions to any extent.

BESNIER-BOECK'S DISEASE

REPORT OF TWO CASES OF EXTENSIVE INVOLVEMENT

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The subject of sarcoid and sarcoid-like tumors has held considerable interest for the dermatologist since Boeck [1] gave his original description of cutaneous sarcoid. The term sarcoid has been rather loosely applied to a number of chronic granulomatous, cutaneous and subcutaneous tumors of diverse etiology. Generally speaking, there are two main types of lesion described under the term sarcoid: (1) cutaneous tumors corresponding to those described by Boeck as multiple benign sarcoid and by Besnier [2] and Tenneson [3] as lupus pernio, and (2) subcutaneous tumors described by Darier and Roussy.[4]

Some authors (Goeckerman,[5] Maloney, Combes [6] and others) expressed the belief that a sharp line of differentiation should not be drawn between the two types of lesions. Goeckerman accepted the unity of cutaneous and subcutaneous sarcoids, basing his theory on similarities of histologic structure and on the belief in a common tuber-

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Read before the Section on Dermatology and Syphilology at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 13, 1936.

1. Boeck, C.: Multiple Benign Sarkoid of the Skin, J. Cutan. Dis. **17**:543-550 (Dec.) 1899.

2. Besnier, E.: Lupus pernio de la face: Synovites fongueuses scrofulo-tuberculeuses symétriques des extrèmitiés supérieures, Ann. de dermat. et syph. **10**:333, 1889.

3. Tenneson: Lupus pernio, Bull. Soc. franç. de dermat. et syph. **3**:421-423, 1892.

4. Darier, J., and Roussy, G.: Des sarcoïdes sous-cutanées, Arch. de méd. expér. et d'anat. path. **18**:1 (Jan.) 1906.

5. Goeckerman, W. H.: Sarcoids and Related Lesions: Report of Seventeen Cases; Review of the Recent Literature, Arch. Dermat. & Syph. **18**:237-262 (Aug.) 1928.

6. Maloney, E. R., and Combes, F. C.: Darier-Roussy Sarcoid, Arch. Dermat. & Syph. **23**:709 (April) 1936.

culous etiology in these conditions. Other authors (Kissmeyer,[7] Pautrier,[8] Nicolas, Massia and Petouraud,[9] Schaumann [10] and Darier [11]) expressed the opinion that they should be differentiated. They expressed the belief that Boeck's sarcoid and lupus pernio are cutaneous expressions of a generalized disease of the reticulo-endothelial system while subcutaneous sarcoid of Darier and Roussy is a localized subcutaneous reaction which, although it may resemble Boeck's sarcoid and lupus pernio clinically and histologically, actually belongs in a separate category.

A wide variety of terminology has been applied to the generalized disease of the reticulo-endothelial system since the original cutaneous manifestations were described by Besnier, Tenneson and Boeck. Besnier named the condition lupus pernio. Boeck [12] noted a similarity between the disease he described and the types of sarcoma or leukemic tumors and for that reason employed the term sarcoid. He shortly thereafter abandoned this term in favor of the designation multiple miliary lupoid when he recognized that the condition belonged in the group of infectious granuloma. Schaumann,[10] who did considerable work on the systemic manifestations of this disease, used the term benign lymphogranulomatosis. Jüngling [13] applied the term ostitis tuberculosa cystica multiplex to the osseous manifestations. Kissmeyer,[7] in his monograph, employed the term Boeck's disease. Pautrier [8] later suggested adding the name Besnier because this author first described one of the manifestations of this condition.

We wish to present two cases of extensive Besnier-Boeck's disease and, if possible, to clarify the widely divergent views regarding the classification and etiology of sarcoid and sarcoid-like tumors. Our cases are of interest because of certain unusual features: 1. Both cases

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7. Kissmeyer, A.: La maladie de Boeck, Paris, Masson & Cie, 1932; Sur l'étiologie des sarcoïdes, maladie spécifique générale, Bull. Soc. franç. de dermat. et syph. **41**:1278-1284 (June) 1934.

8. Pautrier, L. M.: Comment doit se poser la question des sarcoïdes? Bull. Soc. franç. de dermat. et syph. **41**:1002-1010 (June) 1934; La maladie de Besnier-Boeck, ses manifestations cutanées, ganglionnaires, pulmonaires, osseuses, viscérales, nasales et conjonctivales, Presse méd. **43**:146-149 (Jan. 26) 1935.

9. Nicolas, J.; Massia, G., and Petouraud, C.: Les sarcoïdes syphilitiques, J. de méd. de Lyon **14**:295-304 (May 20) 1933.

10. Schaumann, J.: Etude sur le lupus pernio et ses rapports avec les sarcoïdes et la tuberculose, Ann. de dermat. et syph. **6**:357-373, 1917.

11. Darier, J.: Considérations sur la nature des sarcoïdes, Bull. Soc. franç. de dermat. et syph. **41**:999-1002 (June) 1934.

12. Boeck, C., cited by Kissmeyer, A.: La maladie de Boeck, Paris, Masson & Cie, 1932.

13. Jüngling, O.: Ostitis tuberculosa multiplex cystica (eine eigenartige Form der Knochentuberkulose), Fortschr. a. d. Geb. d. Röntgenstrahlen **27**:375, 1920; Ueber Ostitis tuberculosa multiplex cystoides, ein Beitrag zur Lehre von den Tuberculiden des Knochens, Beitr. z. klin. Chir. **143**:401-475, 1928.

occurred in Negroes, an incidence which is exceedingly rare and necessitates the differentiation of Besnier-Boeck's disease from the sarcoid-like lesions of the skin described by Nomland,[14] Klauder and Weidman [15] and others as occurring in American Negroes. 2. Both patients exhibited the seldom reported cystic changes in the long bones as well as in the metatarsals, metacarpals and phalanges. 3. In both instances a biopsy was made on material from one of the cystlike lesions in the long bones; in addition, material from the toe of one of the patients was examined. 4. One patient, a child who had had repeated negative reactions to tuberculin during the early course of Besnier-Boeck's disease, later had positive reactions and subsequently presented clinical evidence of pulmonary tuberculosis associated with negative reactions to tuberculin.

REPORT OF CASES

CASE 1.—A Negro boy aged 13 was first seen in the pediatric wards of the Buffalo General Hospital in January 1932. He complained of blurred vision, photophobia and a purulent nasal discharge of four months' duration. He was well developed and well nourished and did not appear acutely ill. Opacities were present in both corneas. The scleras were injected, and there was a small nodular mass on the nasal side of the left iris. The tonsils were large. No abnormal physical signs were observed in the chest. The liver and spleen were not palpable. No abnormal reflexes were present. The ulnar and posterior auricular nerves were not palpable, and no areas of anesthesia were found. The lymph nodes were markedly enlarged in the postcervical, supraclavicular, axillary and inguinal regions, and they were freely movable and painless. They varied in size from that of a bean to that of a hickory nut. No cutaneous lesions were present. The temperature remained normal during the patient's stay in the hospital.

Intradermal tests with a 1:5,000 and a 1:10,000 dilution of tuberculin were negative on two occasions. The Wassermann and Kahn tests were negative. A lymph node was removed from the posterior cervical region. Many pure epithelioid cell tubercles were present in the node. There was no evidence of necrosis, and giant cells were absent.

Roentgen examination of the chest showed a marked enlargement of the lymph nodes in the hilar region. There was no evidence of tuberculosis in the pulmonary fields.

The patient was discharged from the Buffalo General Hospital to a sanatorium for patients with tuberculosis, a diagnosis of a tuberculous kerato-iritis and tuberculous adenitis being made. He remained in the sanatorium for approximately three months. One week after he was admitted to the institution intradermal tests with 1:1,000 and 1:100 dilutions of tuberculin were negative. A gland was removed from the inguinal region and a guinea-pig inoculated. Tuberculosis failed to develop in the animal.

The patient was admitted to the Buffalo City Hospital in January 1933. At this time he was fairly well nourished and was not acutely ill. There were pannus

14. Nomland, R.: Hematogenous Cutaneous Tuberculosis (Sarcoid) in Negroes: Report of Six Cases, Arch. Dermat. & Syph. **30**:59-75 (July) 1934.

15. Klauder, J. V., and Weidman, F. D.: Multiple Sarcoid-Like Granulomas of the Skin of Undetermined Nature, Arch. Dermat. & Syph. **12**:171 (Aug.) 1925; **13**:675-676 (May) 1926; Ulcerative Sarcoid: A Distinctive Form of Cutaneous Tuberculosis in Negroes, ibid. **31**:421 (March) 1935.

and staphyloma of both corneas, and light perception was absent. A small ulceration was present on the right side of the nasal septum, and a large amount of purulent material was present in the nose. The tonsils were moderately enlarged. The cervical, axillary and inguinal lymph nodes were markedly enlarged. No physical evidence of tuberculosis was observed in the chest. The liver and spleen were not palpable. Fusiform enlargements were present in the fingers, and the bony structure of the knees and elbows was enlarged. There was a generalized

Fig. 1 (case 1).—Roentgenograms showing cystlike areas in the tibias and fibulas.

nodular eruption, the lesions varying from 1 mm. to 3 cm. in diameter and being slightly raised. Small yellowish masses were seen in the nodules on pressure with the diascope. Over some nodules small telangiectatic blood vessels were present. Depigmented areas and areas of atrophic scarring were seen. The lesions were particularly prevalent about the face and buttocks.

The Wassermann and Kahn tests were negative on three occasions. The red blood cells numbered 4,790,000 and the white blood cells 7,900; there was 80 per cent hemoglobin (Sahli). The differential count showed 12 per cent eosinophils, 53 per cent neutrophils, 28 per cent lymphocytes and 7 per cent mononuclears.

The sputum was negative for tubercle bacilli on ten occasions. An intradermal test with a 1 : 10,000 dilution of tuberculin was strongly positive, and a complement fixation test for tuberculosis with the patient's serum was also positive.

Roentgen examinations of the chest showed the pulmonary fields to be clear. The lymph nodes in the hilar region were greatly enlarged. Roentgenograms of the skeleton showed numerous cystlike areas in nearly all the bones of the hands and feet and in the radii, ulnas, humeri, femurs, tibias and fibulas. The skull and the pelvis were normal. The cystlike changes in the long bones were similar to those observed in the smaller bones. They consisted of two types; i. e. (1) large clear

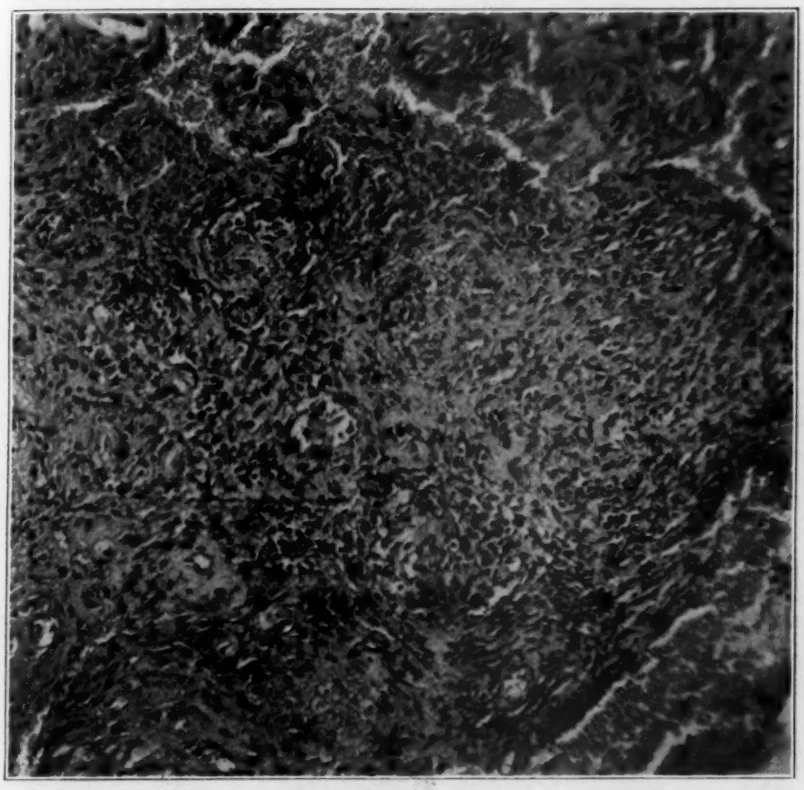

Fig. 2 (case 1).—Photomicrograph of section of bone marrow showing picture of histologic sarcoid.

cystic areas and (2) multiple small loculated areas giving a honeycombed appearance.

Material for biopsy was obtained from a cyst of the lower end of the left radius and from one of the cutaneous nodules. The histologic structure in both instances was essentially the same. Well circumscribed masses of epithelioid cells were present. About the borders there were a moderate sprinkling of lymphocytes and slight fibrosis. No necrosis was noted. The changes in the skin were limited to the corium. Acid-fast bacilli could not be demonstrated in specially stained sections. The histologic picture was similar to that in the lymph node removed in January 1932. Some of the material taken from a cyst in a bone was injected into a guinea-pig. Tuberculosis did not develop. The patient was seen occa-

sionally from January 1933 until August 1935. During that period his condition remained essentially the same.

During March 1936 the patient was again admitted to the Buffalo City Hospital; this time he was acutely ill. He complained of weakness, loss of weight, cough and expectoration.

Physical examination showed extreme emaciation. Both eyes were scarred and atrophic. Signs of infiltration and cavitation were present over the upper lobe of the right lung. The liver and spleen were not felt. The lymph nodes had decreased in size so that they were barely palpable. The cutaneous nodules had entirely disappeared, and only bluish scars marked their previous sites.

Large numbers of tubercle bacilli were observed in the sputum. Intradermal tests with tuberculin gave negative results with dilutions of 1:100, 1:1,000, 1:5,000, 1:10,000, 1:100,000 and 1:1,000,000. Old tuberculin was mixed with

Fig. 3 (case 1).—Photomicrograph of section of lymph node showing masses of epithelioid cells.

the patient's serum in a dilution of 1:5,000 and allowed to stand for twenty-four hours. Tests with this material were made on three other patients known to have positive reactions to tuberculin. The positive result obtained in each instance was as strong as control tests with a 1:5,000 dilution of tuberculin in physiologic solution of sodium chloride. Complement fixation tests for tuberculosis, the patient's serum being used, were negative. Tuberculoproteins were isolated from the urine.[16] They gave positive cutaneous reactions in other patients known to have tuberculosis but failed to cause any reaction in the skin of the patient. The tuberculoproteins obtained from the urine gave positive reactions to complement fixation tests when used as an antigen with the serum of a tuberculinized rabbit. The implication of these observations will be discussed later.

16. Hannan, E. B.: Isolation of a Tuberculin-Like Substance from the Urine of Patients with Active Tuberculosis and Its Practical Application as an Aid in Diagnosis, Arch. Path. **20**:309-310 (Aug.) 1935; personal communication to the authors.

Roentgen examination of the chest showed a large cavity in the upper lobe of the right lung and much infiltration about that area. The hilar glands were much smaller than at the previous examination.

Examination of the bones revealed the same cysts. Progression had taken place in some areas, and healing was evident in others.[16a]

CASE 2.—A Negro aged 56 was first seen at the Buffalo City Hospital in December 1931. At that time he stated that three years before he had frozen his fingers. After this experience his fingers became swollen and somewhat painful. At about the same time he noticed a cutaneous eruption. No family history of tuberculosis was obtained.

The patient presented a generalized eruption consisting of violaceous nodules varying in size from 1 mm. to large plaquelike lesions 4 cm. in diameter. The

Fig. 4 (case 2).—Photograph showing deformity of the hands.

lesions were particularly prevalent on the face. In addition to the nodules, pigmentary macules were present, especially on the trunk, and there were atrophic scars on the extremities. The lymph nodes in the cervical, axillary, epitrochlear and inguinal regions were enlarged. They varied in size from that of a bean to that of a walnut.

The ends of the fingers of both hands were swollen and erythematous and had a boggy consistency. The finger-nails and toe-nails were hypertrophied and crumbling.

A small area of ulceration was present on the right side of the nasal septum. The pharynx revealed no gross abnormalities. The tonsils were moderately

16a. Since this paper was submitted for publication the patient has died of pulmonary tuberculosis. New material taken from the lesions in the bone marrow produced generalized tuberculosis when injected into a guinea-pig. Tubercle bacilli were readily demonstrated in the lesions. Similar material injected into three rabbits failed to produce tuberculosis.

enlarged. The salivary and lacrimal glands were not enlarged. No physical evidence of tuberculosis was present in the chest. The liver and the spleen were not felt. There were no enlargements of the posterior auricular or of the ulnar nerves. No areas of anesthesia were present.

The Wassermann and Kahn tests were negative on three occasions. Intradermal tests with 1:10,000, 1:1,000 and 1:100 dilutions of tuberculin gave negative results. Complement fixation tests for tuberculosis, the patient's serum being used, were negative. Tuberculoproteins were not found in the urine. Tuberculin mixed

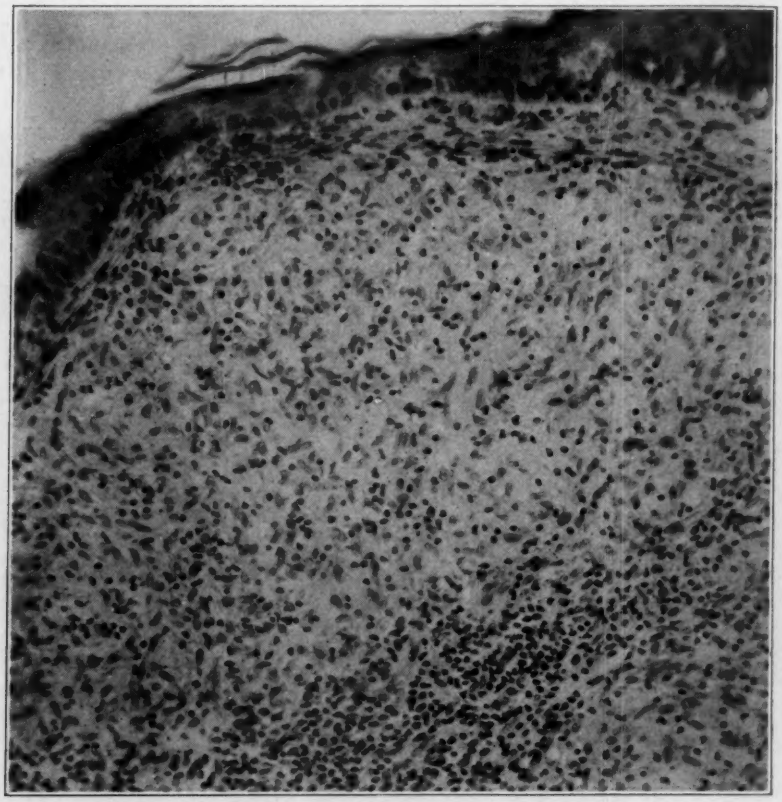

Fig. 5 (case 2).—Photomicrograph of section of cutaneous nodule, showing histologic picture of sarcoid.

with the patient's serum in a 1:5,000 dilution produced just as much cutaneous reaction in patients known to have tuberculosis as did tuberculin mixed with physiologic solution of sodium chloride.

The sputum was negative for tubercle bacilli on twelve occasions. Smears of material from the nose were stained according to the Ziehl-Neelsen technic. The first ten smears gave negative results. The next two contained a few acid-fast bacilli. Twenty-four subsequent smears gave negative results.

Numerous biopsies were made on material from the cutaneous nodules and lymph nodes as well as on that from a cyst of the radius and on that from a small toe. The histologic picture in all instances was essentially the same. It consisted of well circumscribed masses of epithelioid cells, a few lymphocytes and

moderate fibrous tissue hyperplasia. No areas of necrosis were seen. In the skin the pathologic changes were limited to the corium. Numerous sections from all areas stained according to the Ziehl-Neelsen technic failed to reveal tubercle or lepra bacilli.

A guinea-pig inoculated with material aspirated from the nose showed no signs of tuberculosis. Four guinea-pigs were inoculated with emulsified tissue from a lymph node. In none did tuberculosis develop. Two guinea-pigs inoculated with material from the cyst of the right radius showed no signs of tuberculosis. Injection of material from a lymph node into a chicken did not cause tuberculosis. Cultures of material from lymph nodes, from cutaneous nodules and from material aspirated from the finger produced no growth on glycerin agar, Löwenstein's medium or potato agar.

Fig. 6 (case 2).—Roentgenograms showing cystlike changes and absorption in the small bones of the hands.

The blood count revealed no striking abnormalities. The red blood count was 5,430,000 and the white blood count 5,500. There was 76 per cent hemoglobin (Sahli). The differential count showed 64 per cent neutrophils, 21 per cent lymphocytes, 12 per cent monocytes, 2 per cent basophils and 1 per cent eosinophils.

Roentgen examination showed many multiple cystic areas in the small bones of the hands and feet. Similar cystic areas were present in the head of the radius and in the lower third of the shaft of the ulna. The pelvis and spine were normal. The cystic areas were similar in every respect to those observed in case 1.

Because of the presence of acid-fast bacilli in two nasal smears, a diagnosis of leprosy was considered, and the patient was sent to the leprosarium at Carville, La., in September 1932. He was discharged from that institution on March 2, 1933. No evidence of leprosy had been found. The diagnosis was undetermined. Since March 1933 the patient was seen from time to time. His condition remained

essentially the same. The cutaneous lesions disappeared in some areas, and new ones appeared in others. The bony deformities of the hands became more marked. No evidence of tuberculosis developed elsewhere, and tuberculin tests remained negative.

SUMMARY OF CASES

Both patients presented a generalized disease. Lesions were present in the skin, in the lymph nodes, in the nasal mucosa and in the small bones of the hands and feet as well as in certain long bones. The latter location is exceedingly rare. Kissmeyer did not mention it in his mono-

Fig. 7 (case 2).—Roentgenograms showing cystlike changes in the small bones of the feet.

graph. The patient in case 1 also had a kerato-iritis which ultimately resulted in complete blindness with atrophy of the bulbus oculi. Both patients failed to react to tuberculin early in the course of the disease. In case 1 a positive reaction to tuberculin appeared after the patient had gone to a sanatorium for patients with tuberculosis. The reaction became negative again when four and one-half years after the onset of symptoms active pulmonary tuberculosis developed. This patient presented an interesting paradox. Cutaneous anergy (negative reaction to tuberculin) was associated with pulmonary allergy (necrosis, ulceration and cavitation). In case 2 the reaction to tuberculin remained negative, and

no clinical evidence of active tuberculosis developed during eight years of observation. There were no tuberculin-inhibiting substances (anticutines) present in the serum of either patient, and tuberculoproteins capable of producing an allergic response in tuberculous control patients were isolated from the urine in case 1. We therefore believe that the failure of the skin to react to tuberculin in both cases was due to some property of the cutaneous tissue rather than to an immune body present in the patients' serum. We were unable to demonstrate the presence of a causative organism by inoculation of animals or by direct microscopic examination of the skin, lymph nodes and bone marrow. In case 2 cultures gave negative results. We are therefore justified in assuming that viable organisms were not present in the lesions examined. Jacobson [17] has recently reported a case similar to ours occurring in a Negro child. His patient had a conjunctivitis of the left eye and generalized enlargement of the lymph nodes. Cystlike changes were present in the metacarpals and phalanges as well as in the humeri, ulnas, and tibias. A biopsy of material from a lymph node showed a structure identical to that observed in our cases of Besnier-Boeck's disease. Inoculation of material aspirated from one of the lesions in the bone marrow failed to produce tuberculosis in a guinea-pig. During the early period of the disease tuberculin tests were positive. Four years later they became negative. A year and a half later, while the patient was in a sanatorium, she died of tuberculosis. Tuberculin tests became positive before death. Cutaneous lesions were not present at any time. In spite of the absence of cutaneous lesions, Jacobson's case must be classified in the same category as our two cases because of similarities of histologic structure in the lymph node, tuberculin anergy during one period of the disease and identical cystlike changes in the bones as revealed by roentgen examination.

REVIEW OF THE PERTINENT LITERATURE

No unanimity of opinion exists as to the classification and etiology or as to what conditions should be included under the term sarcoid. We shall discuss sarcoid lesions from the experimental, clinical and etiologic point of view.

Experimental Work and Study of the Sarcoid Structure.—Much light has been thrown on the histologic picture of sarcoid by research workers in the field of tuberculosis. Experimental studies with fractional components of tubercle bacilli have shown that the epithelioid cell response (sarcoid-like reaction) is due to the presence of lipoids and waxlike substances present in the bacilli.

17. Jacobson, W.: Generalized Tuberculosis of the Lymph Nodes and Multiple Cystic Tuberculosis of the Bones, J. Pediat. **8**:292-307 (March) 1936.

Ray and Shipman [18] have shown that similar substances are present in grass and in colon bacilli. They have produced sarcoid-like lesions in experiments with lipoids derived from these organisms. Anderson [19] isolated an alcohol-soluble lipoid containing phosphorus which he called phosphatide. Sabin [20] produced pure epithelioid cell responses with this material (experimental sarcoid). Krause [21] pointed out that in nontuberculous animals the first tissue response to the presence of living or dead tubercle bacilli is an epithelioid cell reaction. This is later altered by signs of inflammation and necrosis when allergy to tuberculoproteins develops. He stated that the elementary epithelioid cell tubercle, unaltered by allergy, is the native response of animal tissues to all substances which they are not equipped to absorb, dissolve or disintegrate in other ways. Sabin [20] stated that the reaction to phosphatide produces such pure epithelioid cell responses that it is possible to speak of phosphatide disease or of the phosphatide element of tuberculosis. She and her co-workers [22] have experimentally produced pure epithelioid cell tubercles, a reaction similar to sarcoid, in roosters by injection of a smooth strain of avian tubercle bacilli. The birds died of tuberculosis but exhibited no tissue allergy to tuberculoproteins. Werner Jadassohn [23] has produced sarcoid-like lesions in the skin of rats by injection of tubercle bacilli. The animals do not exhibit allergy to tuberculoproteins.

The work of these investigators demonstrates that experimental epithelioid responses (sarcoid-like lesions) depend on two factors: (1) the presence of insoluble foreign substances such as lipoids and waxes present in certain living or dead organisms or in the pure state, and (2) the absence of tissue allergy to the other components of the organisms. The sarcoid-like histologic picture is not a specific response to the presence of the tubercle bacillus but may be produced by materials derived from other organisms. It does not necessitate the presence of viable organisms, since dead tubercle bacilli produce a similar response in nonallergic animals.

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18. Ray, L. W., and Shipman, J. S.: Studies on Biochemistry Produced by Action of Lipins of Tubercle, Grass and Colon Bacilli, and of Liver, Am. Rev. Tuberc. **7**:88-104 (April) 1923.

19. Anderson, R. J.: Separation of Lipoid Fractions from Tubercle Bacilli, J. Biol. Chem. **74**:525-535 (Sept.) 1927; Study of Phosphatide Fraction of Tubercle Bacilli, ibid. **74**:537-551 (Sept.) 1927.

20. Sabin, F. R.: Cellular Studies in Tuberculosis, Am. Rev. Tuberc. **25**: 153-171 (Feb.) 1932.

21. Krause, A. K.: Anatomical Structure of Tubercle from Histogenesis to Cavity, Am. Rev. Tuberc. **15**:137-168 (Feb.) 1927.

22. Sabin, F. R.; Miller, F. R.; Doan, C. A., and Wiseman, B. K.: Study of Toxic Properties of Tuberculo-Proteins and Polysaccharides, J. Exper. Med. **53**: 51-80 (Jan.) 1931.

23. Jadassohn, W.: L'origine tuberculeuse de la maladie de Boeck, Bull. Soc. franç. de dermat. et syph. **41**:1344-1347 (June) 1934.

Clinical Observation on Sarcoid Lesions.—The experiments with animals made by research pathologists have been borne out by clinical experience. Cutaneous and subcutaneous nodules having a histologic structure like that of sarcoid have been produced by diverse causes. Kyrle,[24] Wende,[25] Dittrich,[26] Ruete [27] and Hudelo, Montlaur and LeForester [28] have observed acid-fact bacilli, believed to be tubercle bacilli, in sarcoid lesions of the skin in man. Pautrier,[29] Motta,[30] Filho [31] and others, have seen sarcoid lesions due to leprosy. Frazier and Hu [32] have isolated Spirochaeta pallida from a sarcoid-like lesion, and Pautrier,[8] Stein,[33] Nicolas, Massia and Petouraud,[9] Darier,[11] Gougerot [34] and others have expressed the belief that in some cases sarcoid is syphilitic. Gougerot [34] and Darier [11] expressed the opinion that in certain cases sarcoid is due to foreign bodies. Dupont [35] has reported a case of leishmaniasis in which there was a histologic structure typical of sarcoid. It is evident from these clinical observations that sarcoid-like lesions can be produced by many causes.

Dermatologists disagree as to what clinical manifestations should be included under the term sarcoid. The disagreement is largely a matter of definition. Goeckerman [5] stated that when some cause other than tuberculosis is known to have produced a sarcoid-like lesion, the disorder should not be classified as sarcoid. Maloney and Combes [6]

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24. Kyrle, J.: Die Anfangsstadien des Boeckschen Lupoids: Beitrag zur Frage der tuberkulösen Aetiologie dieser Dermatose, Arch. f. Dermat. u. Syph. **131**: 33-79, 1921.

25. Wende, G.: Nodular Tuberculosis of the Hypoderm, J. Cutan. Dis. **29**:1-7 (Jan.) 1911.

26. Dittrich, O.: Ueber den direkten Tuberkelbazillen nachweis beim Lupus pernio und beim Sarkoid Boeck, Dermat. Ztschr. **60**:395-403 (April) 1931.

27. Ruete, A.: Zur Aetiologie der Boeckschen Erkrankung, Dermat. Ztschr. **37**:129-136, 1922.

28. Hudelo; Montlaur, and LeForester: Lymphogranulomatose de Schaunnaun (lupus pernio) à forme anormale, Bull. Soc. franç. de dermat. et syph. **32**: 109-112 (March) 1925.

29. Pautrier, L. M.: Léprome à histologie de sarcoïde dermique, Bull. Soc. franç. de dermat. et syph. **41**:1284-1291 (June) 1934.

30. Motta, J.: Les sarcoïdes de la lèpre, Ann. de dermat. et syph. **2**:1180-1187 (Nov.) 1931.

31. Filho, R., in Etiology of Besnier-Boeck's Disease, Foreign Letter, J. A. M. A. **105**:1205 (Oct. 12) 1935.

32. Frazier, C. N., and Hu, C. K.: Isolation of Treponema Pallidum from Subcutaneous Sarcoid, Proc. Soc. Exper. Biol. & Med. **30**:898-901 (April) 1933.

33. Stein, L. J.: Contribution à la question concernant l'origine syphilitique de la sarcoïde de Boeck, Rev. franç. de dermat. et de vénéreol. **9**:168-173 (March) 1933.

34. Gougerot, H.: Sarcoïdes: Syndrome et adjectif. Multiplicité des causes; fréquence de la tuberculose, Bull. Soc. franç. de dermat. et syph. **41**:1017-1021, (June) 1934.

35. Dupont, A.: Un cas de bouton d'orient à structure de sarcoïde de Boeck, Ann. de dermat. et syph. **1**:453-461 (May) 1930.

recently stated that Darier-Roussy's sarcoid is tuberculous but that there is a condition clinically and histologically indistinguishable from it due to diverse causes. If one accepts the limitations imposed by these authors and defines sarcoid as a tuberculous disease which may be mimicked clinically and histologically by lesions produced by other causes, into what etiologic group can one place those disorders of unknown etiology? The latter group makes up by far the great majority of cases. We were able to gather from the American literature of the last ten years one hundred and fourteen cases in which the condition was diagnosed as sarcoid. Tubercle bacilli were not observed in any of the lesions, and evidence of tuberculosis in other organs was noted in only seven cases. We therefore disagree with authors who define sarcoid as a special clinical and histologic response to the bacillus of Koch. We believe, as have Darier,[11] Gougerot,[34] Pautrier [8] and others, that the term sarcoid should include clinical and histologic syndromes of diverse etiology and that in cases in which the etiology is unknown one is not justified in accepting a single etiologic cause, such as tuberculosis.

Clinical Classification of Sarcoid.—Pautrier [8] expressed the belief that widely diverse clinical conditions have been classified under the term sarcoid. There are three main types:

Type 1: This is a form of cutaneous tuberculosis with small miliary nodules from the size of a millet seed to that of a pea. Glandular enlargement is common. The condition is called by French authors *lupoïde miliaire.*[36] Histologically the lesions are in the corium; some show necrosis, and others have a typical sarcoid structure and thus may mimic the dermal manifestations of type 3, or Besnier-Boeck's disease. Tuberculin tests may or may not be positive. We agree with Pautrier and others that this disease is distinct from true Besnier-Boeck's disease. It differs in its tendency to necrosis, in the fact that frequently tuberculosis is present elsewhere, in that tubercle bacilli are observed in the lesions and in that generalized systemic manifestations are absent. Schaumann [37] expressed the belief that this condition was first described by Tilbury Fox under the term disseminated follicular lupus, and he agreed with Pautrier that it is a form of cutaneous tuberculosis belonging in the catebory of lichen scrofulosorum and the papulonecrotic tuberculids. Nicholas and Gaté [38] concurred in this view. The disorder appears to be closely related to a tuberculous cutaneous disease of Negroes

36. Pautrier, L. M.: La lupoïde miliaire des auteurs français doit être détachée du groupe des sarcoïdes dermiques et rattachée franchement à la tuberculose cutanée, Bull. Soc. franç. de dermat. et syph. **41**:1027-1054 (June) 1934.

37. Schaumann, J.: Sur quelques dermatoses non attribuables à la lymphogranulomatose bénigne, Bull. Soc. franç. de dermat. et syph. **41**:1322-1326 (June) 1934.

38. Nicolas, J., and Gaté, J.: A propos des sarcoïdes, Bull. Soc. franç. de dermat. et syph. **41**:1011-1017 (June) 1934.

reported in this country under various names, such as multiple sarcoid-like granuloma, ulcerative sarcoid (Klauder and Weidman [15]), hematogenous cutaneous tuberculosis or sarcoid in Negroes (Nomland [14]), lupus miliaris disseminatus (Tauber and Goldman [39]), disseminated miliary tuberculosis of the skin (Busman [40]) and cutaneous nodulodiscoid tuberculosis of the anergic type (Crawford [41]).

Type 2: The second group of lesions commonly called sarcoid is that described by Darier and Roussy. Clinically the lesions are deep seated rather than dermal, as in types 1 and 3, and relatively few lesions are present. The disorder has seldom been reported in association with the systemic manifestations of Besnier-Boeck's disease (type 3). Schaumann [37] stated that in rare instances the infiltrate seen in Besnier-Boeck's disease may extend hypodermally, but he did not regard cases in which this occurs as instances of Darier-Roussy sarcoid. Kissmeyer [7] did not mention this development in his monograph on Boeck's disease. Schaumann expressed the belief that erythema induratum belongs in this group, and Kissmeyer admitted that a close relationship exists between the two conditions. Histologically Darier-Roussy sarcoid resembles Besnier-Boeck's disease, except that in the latter condition the infiltrate is in the corium. We believe that this type should be differentiated from type 1 and type 3 by the dermal manifestations, the absence of systemic findings and the hypodermal location of the infiltrate in histologic sections. We admit that from the cutaneous manifestations alone it may occasionally be difficult to differentiate Darier-Roussy's sarcoid from the cutaneous manifestations of Besnier-Boeck's disease. From the etiologic standpoint, Darier-Roussy's sarcoid appears to be a syndrome of diverse etiology.

Type 3: The third type, or Besnier-Boeck's disease, is characterized in its dermatologic aspect by the various manifestations of Boeck's sarcoid or of lupus pernio. The disease is not primarily one of the skin but rather a generalized reticulo-endotheliosis characterized by multiple dermal manifestations, by generalized lymphadenopathy and by the presence of similar lesions in the lungs, bone marrow, nasal mucosa, conjunctivae, corneas, lacrimal and salivary glands, liver and spleen. In our two cases the disorder was of this type. As already mentioned, the dermal manifestations of this type of sarcoid are sometimes indistinguishable from those of types 1 and 2. Diagnosis frequently depends on the multiple accessory observations mentioned.

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39. Tauber, E. B., and Goldman, L.: Systemic Phase of Tuberculosis Cutis, Arch. Dermat. & Syph. **27**:295-301 (Feb.) 1933.

40. Busman, G. J.: Disseminated Miliary Tuberculosis of the Skin, Arch. Dermat. & Syph. **25**:194 (July) 1932.

41. Crawford, S.: Cutaneous Nodulodiscoid Tuberculosis of Anergic Type with Development into Active Pulmonary Tuberculosis, Arch. Dermat. & Syph. **27**:766-777 (May) 1933.

Etiology—There is a divergence of opinion concerning the etiology of Besnier-Boeck's disease. Briefly there are three schools of thought: (1) Some observers accept a tuberculous etiology. (2) Some believe that the condition is a specific disease of unknown etiology. (3) Some believe that two or more diseases are capable of producing the same clinical and histologic picture, for example tuberculosis and leprosy.

Jadassohn,[23] Martenstein,[42] Volk,[43] Jüngling,[13] Kyrle, [24] Schaumann,[44] Sulzberger [45] and many others, have considered the condition to be tuberculous, but there has been scant direct laboratory evidence supporting this belief. The view that it is tuberculous is based on the tuberculoid histologic changes, the rare observation of acid-fast bacilli in sarcoid lesions of the skin or other organs, the results of inoculation experiments and certain biologic phenomena, such as the absence of the reaction to tuberculin and the presence of anticutins (substances which neutralize tuberculin) in the serum of these patients.

Bacilli have been noted by a few observers in dermal sarcoid-like lesions. Kyrle observed bacilli in a lesion of Boeck's sarcoid eleven days old but was unable to produce tuberculosis in guinea-pigs inoculated with material from the lesions. He expressed the belief that the tubercle bacilli were already dead. Dittrich [26] and Ruete [27] also observed acid-fast bacilli in the lesions of dermal sarcoid. Neither proved them to be viable tubercle bacilli by inoculation experiments. Hudelo, Montlaur and LeForester [28] observed acid-fast bacilli in giant and interstitial cells of a lesion of lupus pernio and were able to produce a caseous node in a guinea-pig in which acid-fast bacilli were observed. They were unable to culture the organism from the lymph node.

In the past few years reports by Van Alstyne and Gowen,[46] Vastine and Bacon,[47] Chisholm [48] and others have appeared in the American literature on Jüngling's disease of the long bones. Tubercle bacilli were readily demonstrated in most of these cases. However, none of

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42. Martenstein, H.: Sarcoid of Boeck and Lupus Pernio, Arch. f. Dermat. u. Syph. **147**:70-99, 1924.

43. Volk, R.: Zum Sarcoid Boeck, Arch. f. Dermat. u. Syph. **138**:327, 1922.

44. Schaumann, J.: Observations cliniques, bactériologiques, et sérologiques pour servir à l'étiologie de la lymphogranulomatose bénigne, Bull. Soc. franç. de dermat. et syph. **41**:1296-1322 (June) 1934.

45. Sulzberger, M. B.: Sarcoid of Boeck (Benign Miliary Lupoid) and Tuberculin Anergy: Report of a Case and General Remarks, Am. Rev. Tuberc. **28**:734-745 (Dec.) 1933.

46. Van Alstyne, G. S., and Gowen, G. H.: Osteitis Tuberculosa Multiplex Cystica (Jüngling): Report of a Case Involving the Larger Bones with Complete Proof of Its Tuberculous Etiology; Review of the Literature, J. Bone & Joint Surg. **15**:193-205 (Jan.) 1933.

47. Vastine, J. H., and Bacon, E. P.: Osteitis Tuberculosa Multiplex Cystica, with Report of Two Cases, Radiology **24**:22-30 (Jan.) 1935.

48. Chisholm, D. R.: Case of Osteitis Tuberculosa Multiplex Cystica, Canad. M. A. J. **32**:302-304 (March) 1935.

the patients had the small honeycombed cysts observed in the long bones of our patients or the characteristic cysts of the small bones. The manifestations reported by these authors were not associated with the generalized changes of Besnier-Boeck's disease. In most instances they were associated with outspoken tuberculosis elsewhere. In their cases biopsy material taken from the cysts in the bone had a histologic structure typical of tuberculosis. Petter and Medelman [49] reported eight cases of such conditions observed in a sanatorium for patients with tuberculosis under the name tuberculosis of the shaft of the long bones. We do not believe that in these cases the condition represented the osseous manifestations of Besnier-Boeck's disease, and therefore the observations cannot be taken into consideration in an attempt to establish the etiology of the latter condition.

Inoculation experiments in cases of Besnier-Boeck's disease have given almost uniformly negative results. Gans [50] obtained a positive result of inoculation in a guinea-pig in one case, but the patient from whom material was obtained had obvious tuberculosis. Jüngling [13] reported positive results of inoculation of a guinea-pig with material from a patient whom he described as having ulcerative sarcoid. The animal survived for a period of seven months. Ravaut, Valtis and Nélis [51] inoculated six guinea-pigs with material from a lesion of Boeck's sarcoid of the skin. The guinea-pigs remained healthy, but on post-mortem examination acid-fast bacilli were observed in the tracheobronchial nodes. The organisms were not proved to be tubercle bacilli. Kissmeyer stated that similar organisms are present in normal guinea-pigs. Ramel [52] has reported positive results of inoculations of guinea-pigs, tuberculosis developing after three or four passages. In such instances cage infection must be seriously considered. Calmette [53] stated that this occurs more commonly than is supposed.

Patients with sarcoid lesions rarely show evidence of tuberculosis elsewhere. Allison and Mikell,[54] Goeckerman,[5] Jacobson,[17] Keck and Micha-

49. Petter, C. K., and Medelman, J. P.: Tuberculosis of Shafts of Long Bones: Clinical and Roentgenological Study with Report of Eight Cases, Am. Rev. Tuberc. **32**:285-293 (Sept.) 1935.

50. Gans, O.: Ueber Lupus pernio und seine Beziehungen zum Sarcoid Boeck, Dermat. Ztschr. **33**:64-80, 1921.

51. Ravaut, P.; Valtis, J., and Nélis, P.: Résultats de l'inoculation au cobaye d'une sarcoide et d'une tuberculide papulo-nécrotique, Compt. rend. Soc. de biol. **101**:444 (June 14) 1929.

52. Ramel, E.: D'un "lupus pernio" (type Schaumann), probablement déterminé par un bacille tuberculeux de type bovin, Bull. Soc. franç. de dermat. et syph. **41**:1332-1344 (June) 1934.

53. Calmette, A.: L'infection tuberculeuse spontanée du cobaye et du lapin, Rev. de la tuberc. **1**:113-125 (Feb.) 1933.

54. Allison, J. R., and Mikell, P. V.: Sarcoid Associated with Tuberculosis of the Larynx: Report of a Case, Arch. Dermat. & Syph. **25**:334-343 (Feb.) 1932.

lik [55] and Schaumann [44] have reported cases in which sarcoid was associated with active systemic tuberculosis. Kissmeyer [7] found in a survey of the literature that 10 per cent of one hundred and fifty patients with Besnier-Boeck's disease presented evidence of tuberculosis in other organs. Of thirty-five patients whom he observed, one died of tuberculosis and two others had evidences of healed pleurisy. Of one hundred and fourteen cases gathered by us from the American literature, tuberculosis was present in other organs in approximately 6 per cent.

Most observers agree that the reaction to tuberculin is frequently negative in patients with Besnier-Boeck's disease. This has been interpreted by Jadassohn,[23] Martenstein,[42] and others as indicating positive anergy. It is believed that this state of anergy explains the peculiar histologic structure of the lesions of Besnier-Boeck's disease. These same authors stated that anticutins are present in the serum of patients with Besnier-Boeck's disease and that this explains the common occurrence of negative reactions to tuberculin among patients with this disorder. We were unable to demonstrate any tuberculin-inhibiting substance in the serum of our patients.

Kissmeyer,[7] Lomholt [56] and others expressed the belief that Besnier-Boeck's disease is a specific disease of unknown etiology and pointed to the infrequent presence of tubercle bacilli in histologic sections, to the results of inoculation experiments and of cultures, to the relative infrequency of tuberculosis in other organs and to the failure of the lesions to flare up after injections of tuberculin. They considered the negative reactions to tuberculin to be against a tuberculous etiology and argued that the explanation based on a theory of anergy is highly theoretical. Lomholt stated that the osseous manifestations are never observed in true tuberculosis and that chaulmoogra oil causes healing of the lesions of Besnier-Boeck's disease but is without effect on true tuberculous lesions such as lupus vulgaris.

Filho [31] pointed out that the whole syndrome of Besnier-Boeck's disease can be produced by leprosy, including the sarcoid-like dermal lesions, generalized lymphadenopathy, rhinitis, cystic changes in the bones, histologic picture and tuberculin anergy. Many authors have described typical dermal lesions of sarcoid produced by the lepra

55. Keck, A., and Michalik: Untersuchungen über einen Tuberkelbazillenstamm aus der Lunge einer Patientin mit Boeckschen Sarkoid, Dermat. Wchnschr. **80**:429-432, 1925.

56. Lomholt, S.: Discussions et conclusions sur la conception du groupe des sarcoïdes dermiques et sur leur étiologie, Bull. Soc. franç. de dermat. et syph. **41**: 1350-1353 (June) 1934; Douze cas de sarcoïdes de Boeck traités à l'antiléprol, ibid. **41**:1354-1362 (June) 1934.

bacillus. Keratitis [57] is not an uncommon finding among patients with leprosy. Murdoch and Hutter [58] have described cystic changes in the bones occurring in patients with leprosy which they called osteitis leprosa cystoides multiplex and which duplicate all the essential changes observed in the bones of patients with Besnier-Boeck's disease. Chevallier and Fiehrer [59] and Nielsen [60] also spoke of these changes as occurring in lepers. Murdoch and Hutter [61] have also noted sandpaper mottling of the lungs not dissimilar to that observed in patients with Besnier-Boeck's disease. Leprosy is therefore capable of producing most, if not all, of the important clinical and histologic changes of Besnier-Boeck's disease.

After carefully reviewing the literature and observing our two cases, we believe that Besnier-Boeck's disease is not a specific condition but is due to at least two causes, namely, tuberculosis and leprosy. The histologic picture depends on the presence of lipoid and waxlike substances present in relatively large amounts in all acid-fast organisms.

SUMMARY

Two cases of extensive Besnier-Boeck's disease observed for four and one-half and eight years, respectively, are reported.

The same histologic changes were present in the skin in the lymph nodes and in the bone marrow of the long and short bones.

In case 1 pulmonary tuberculosis developed four and one-half years after the onset of Besnier-Boeck's disease. Tuberculin tests were negative during the early stages of Besnier-Boeck's disease and during the period of active pulmonary tuberculosis. The anergy was positive and could not be attributed to the presence of anticutins because these could not be detected in the patient's serum and active tuberculoproteins were found in the urine. We believe from a study of this case that tuberculosis was responsible for the development of Besnier-Boeck's disease.

In case 2 there was at no time clinical or laboratory evidence of tuberculosis or of leprosy. The osseous manifestations were unusually severe and extensive.

57. Pfingst, A. O.: Ocular Complications of Leprosy, Am. J. Ophth. **9**:195-196 (March) 1926.

58. Murdoch, J. R., and Hutter, H. J.: Leprosy: Roentgenological Survey, Am. J. Roentgenol. **28**:598-621 (Nov.) 1932.

59. Chevallier, P., and Fiehrer, A.: La polydactylite pseudokystique pure (ou polyostéite nodulaire pseudokystique primitive des extrémités). Ses rapports avec le syndrome identique secondaire à des sarcoïdes. Contribution à l'étude de la polyostéite pseudokystique ("Ostitis tuberculosa multiplex cystoides") maladie de Perthès-Jüngling, Bull. Soc. franç. de dermat. et syph. **41**:1144-1186 (June) 1934.

60. Nielsen, J.: Recherches radiologiques sur les lésions des os et des poumons dans les sarcoïdes de Boeck, Bull. Soc. franç. de dermat. et syph. **41**:1187-1218 (June) 1934.

61. Murdoch, J. R., and Hutter, H. J., cited by Nielsen.[60]

We believe that from the clinical standpoint sarcoid-like lesions should be differentiated into three types: (*a*) tuberculids, similar to the miliary lupoid described by French authors and to disseminated sarcoid-like lesions observed in American Negroes; (*b*) Darier-Roussy's, or hypodermal, sarcoid; (*c*) Besnier-Boeck's disease.

From the etiologic standpoint, sarcoid-like lesions may be produced by diverse agents. The histologic reaction depends on two factors: (*a*) suitable foreign bodies, such as lipoids and waxlike substances present in certain organisms, and (*b*) absence of tissue allergy in the host.

Besnier-Boeck's disease appears to be a syndrome capable of being produced by at least two causes, tuberculosis and leprosy.

ABSTRACT OF DISCUSSION

Dr. J. P. Guequierre, Philadelphia: I am impresed with the tremendous amount of clinical work and study which this paper represents, and I particularly appreciate the thorough histologic studies. The authors have shown that in the past too much emphasis has been placed on tuberculosis as the etiologic agent, and I agree with them that in cases in which the etiology is unknown one is not justified in considering tuberculosis as the single cause. The experimental production of histologic changes like those of sarcoid or sarcoid-like lesions by injections of foreign substances indicates that the changes may be a nonspecific tissue response produced by tuberculosis, syphilis, leprosy or other agents. In view of this, and because an intercurrent infection may light up an old tuberculous focus, should one say that tuberculosis was responsible for the development of Besnier-Boeck's disease in case 1 or that the long-continued presence of Besnier-Boeck's disease activated a latent tuberculous infection in that case? Certainly more research work is indicated along experimental lines in the biochemical field. For example, more light may be shed on this disease and also on the interrelation of some other dermatoses, such as lupus erythematosus, and possibly on tuberculosis itself. It is possible that roentgenograms of the bones made as a routine will reveal cystic changes more frequently than has been the case heretofore.

Hunter brought out the point that this disease offers a possible solution to another problem, "that of apparently healthy patients without skin lesions having increased hilus shadows accompanied by diffuse infiltration, an appearance not infrequently diagnosed as tuberculosis." He suggested that "more careful roentgen and clinical observations may in the future determine whether these patients are suffering from sarcoid disease." It may be well to bring this point to the attention of roentgenologists. Greenbaum, who is working on Besnier-Boeck's disease, agreed with Kissmeyer that in time this condition will be considered a disease sui generis. He called it "sarcoidosis," meaning sarcoid disease, to differentiate it from sarcoid of tuberculous, leprous or syphilitic origin.

Dr. Marion B. Sulzberger, New York: I think that the conclusions of Drs. Jordon and Osborne are in the main in agreement with the opinion at present held by a majority of observers as to the origin of this type of histologic picture, namely, that it represents a certain state of immunologic response and that it may therefore be due to various etiologic factors. However, I believe that it is accepted by the vast majority of careful students of cutaneous tuberculosis that the etiology of this type of histologic response is—at least in the majority of instances—the tubercle bacillus. I see nothing in the presentation of Drs. Jordon

and Osborne that might make a change in that concept. The proof that in most instances of sarcoid the tissue reaction is actually due to tuberculosis is by no means easy to establish. It is based, among other evidence, on a specific alteration in response to tuberculin, on the fact that tubercle bacilli are present in some focus in most cases of sarcoid, on the observation that lupus vulgaris has been known to change to sarcoid and on the fact that in both of these types of transformation the response to tuberculin has often changed from anergy to a hypersensitivity, or vice versa, the change corresponding to the histologic change of structure. I would take issue with the conclusions of Dr. Sabin and other workers who say that they have isolated the epithelioid cell-producing fraction of the tubercle bacillus. If fat, paraffin or beeswax is injected into the skin, tuberculoid and occasionally sarcoid structures will be produced. Dr. Sabin has taken fatty extracts in large quantities, such as can be extracted only from large quantities of tubercle bacilli, and injected them, and thus he has produced foreign body tubercles and epithelioid cells. I believe that one must admit that the sarcoid and tuberculoid reactions, when produced by micro-organisms, are histologic expressions of a certain form of immunologic response. There seems to be no other explanation possible when one considers, on the one hand, that the injection of tubercle bacilli in rats produces sarcoid structures while the tubercle bacilli are being rapidly destroyed or attenuated by the natural immunity of the rat (Werner Jadassohn), and, on the other hand, that the injection of those same tubercle bacilli with the same chemical constituents and the same quality of lipoid into guinea-pigs, which are not immune to tuberculosis, does not produce sarcoid structures. In other words, the formation of tuberculoid structures must be dependent in the main on the immunologic reaction of the tissues and not on the chemical constituents of the injected substance. This point is clinched by the fact that guinea-pigs in which immunologic reactions have become altered later also exhibit tuberculoid structures as a result of injection of the same bacilli (superinfection or reinfection) or as later manifestations of primary infection. Furthermore, sarcoid and tuberculoid, i. e., tubercle-like structures, may result from a great variety of micro-organisms. Such structures can be produced even by virus, such as the Frei virus. They are a not uncommon reaction to leprosy bacilli. They are often observed after injections of trichophytin, and I have seen them develop even after injections of trichophytin polysaccharide. They are frequently seen in older sites of injections of tuberculin or of Frei vaccine, and they can arise from a great variety of infectious processes and follow all types of injections. I believe that all this is further evidence supporting the well known law expressed by Jadassohn and Lewandowsky. Wherever micro-organisms are being rapidly destroyed by the immune processes of the tissues, tuberculoid and epithelioid cell reactions may result. One is therefore forced to a conclusion which coincides closely with that of Drs. Jordon and Osborne. While one must bear in mind that sarcoid reactions are usually tuberculous, theoretically they are characteristic of a certain immune state and cannot, therefore, be pathognomonic or diagnostic of one etiologic agent to the exclusion of other possible etiologic factors.

Dr. Moses Scholtz, Los Angeles: Discussion on sarcoid is of interest not only because of its clinical significance but also because it reveals some limitations and weaknesses of the basic principles controlling the present technic of morphologic differentiation and the present classification. Because of time limitations I restrict myself to one point, differentiation of sarcoid from tuberculid and particularly differentiation of one type of tuberculid from the other. It is hard to understand why one should need so many names and subdivisions to designate clinical forms which have the same morphologic pattern and the same pathogenesis

and which call for the same kind of treatment. The demand to differentiate clearly such conditions as miliary lupoid, papulonecrotic tuberculids, miliary disseminated lupus, acne agminata, acnitis and follicles seems to me artificial and superfluous. It seems also that morphologic difficulties are due to the fact that dermatologists still retain the old botanical static conception of a morphologic entity as something stationary, a conception which implies that the dermatologic entity should retain its morphologic pattern throughout the whole course of the disease. In direct opposition to this static conception, I propose the dynamic conception of cutaneous morphology. I consider dermatoses as cutaneous reactions which are capable of change and mobility, reactions that may be superimposed on or combined with, one another and finally undergo complete morphologic transformation of one entity into the other. The rationale and the plea for the dynamic conception of cutaneous morphology were offered for consideration in the last issue of the ARCHIVES. At present these ideas may be considered radical and iconoclastic. I am sure, however, that as time goes on they will be accepted as a biologically correct and clinically rational explanation of the present morphologic complexities. I believe also that this will simplify and clarify many of the difficult problems of dermatologic nomenclature. From this dynamic point of view, sarcoid would appear to be a specialized cutaneous reaction which can be produced by several agents, of which tuberculosis is the most common and important.

DR. JAMES W. JORDON, Buffalo: Dr. Osborne and I believe that tuberculosis was responsible for the entire syndrome observed in case 1, and we base our belief on the persistence of cutaneous anergy to tuberculosis during the period when the patient had active pulmonary tuberculosis and on the presence of many tubercle bacilli in the sputum. We were able to find only one other case in the literature in which active tuberculosis developed after Besnier-Boeck's disease and cutaneous anergy to tuberculin persisted. The case presents an interesting paradox, namely, cutaneous anergy associated with pulmonary allergy (a negative cutaneous reaction to tuberculin associated with ulceration and cavitation in the lungs). We further believe that the theory that tuberculosis was responsible for Besnier-Boeck's disease in this case is strengthened by the presence in the urine of tuberculoproteins to which the patient's skin did not react but which produced in other patients with tuberculosis a cutaneous reaction similar to that observed after tuberculin tests. The subsequent development of active tuberculosis in cases of Besnier-Boeck's disease is a rare phenomenon. Schaumann has reported three cases of such manifestations, and a few other observers have reported cases of proved active tuberculosis developing after sarcoid-like lesions had been present in the skin. We cannot agree with Dr. Sulzberger that tubercle bacilli can usually be observed in sarcoid lesions if the lesions are extensively examined. Few observers have observed acid-fast bacilli in cutaneous lesions of sarcoid. Kyrle, Ruete and Dittrich observed acid-fast organisms but were unable to prove them to be viable tubercle bacilli by either inoculation of animals or culture. There is only one case reported in the literature in which bacilli were observed in lesions and inoculation of animals was successful, namely, that of Hudelo, Montlaur and LeForester. These authors were able to produce a caseous node in a guinea-pig by inoculation of tissue taken from a lesion of lupus pernio which they described as being abnormal They observed acid-fast bacilli on microscopic examination of the tissue. We believe that in the majority of cases sarcoid lesions as seen in this country are tuberculous, but we believe that other conditions can produce a similar syndrome. Darier himself expressed the belief that the sarcoid which he described in collaboration with Roussy can be produced by multiple agents.

LXXVII.—EARLY ACUTE LUPUS ERYTHEMATOSUS

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Acute disseminated lupus erythematosus, although a relatively infrequent disease, has been the subject of frequent discussion in dermatologic literature. In 1931 Mook, Weiss and Bromberg [1] covered the present knowledge rather thoroughly. Recently Baehr, Klemperer and Schifrin [2] reported and analyzed twenty-three cases. The cause of the disease and its actual mechanism, however, remain a subject of controversy. The fully developed picture of the acute illness, the typical cutaneous eruption and the usual autopsy observations are fairly definite and familiar. It is the earliest phases of the disease that are vague and indefinite.

The earliest recognizable symptom is the erythema. There may be preceding or accompanying constitutional symptoms, but these probably are of such general nature that unless the erythema suggests the diagnosis lupus erythematosus will not be suspected. In this connection it is noteworthy that Baehr, Klemperer and Schifrin [2] mentioned cases in which the constitutional manifestations and autopsy observations were similar to those in cases of acute disseminated lupus erythematosus and yet no cutaneous lesions ever developed. Probably acute lupus erythematosus is a constitutional disease in which cutaneous erythema is entirely of a secondary character and is perhaps not always present, at least in the earliest phases.

The following cases are reported with the purpose of calling attention to the early cutaneous and constitutional symptoms.

REPORT OF CASES

CASE 1.—J. C. T., a girl aged 17, was a student in a large private school. She was active in athletic and social affairs. The summer of 1935 had been particularly strenuous. On Oct. 13, 1935, the patient had an attack of urticaria.

Read at the Fifty-Ninth Annual Meeting of the American Dermatological Association, Inc., Swampscott, Mass., June 6, 1936.

Studies, observations and reports from the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, service of Dr. M. F. Engman.

1. Mook, W. H.; Weiss, R. S., and Bromberg, L. K.: Lupus Erythematosus Disseminatus, Arch. Dermat. & Syph. **24**:786-829 (Nov.) 1931.

2. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis), Tr. A. Am. Physicians **50**:139-152, 1935.

Both left eyelids, especially the lower, were red and swollen. There was a large wheal over the right cheek, and similar patches of urticaria were present on the right ear and on the right cubital space. Injection of 5 minims (0.305 cc.) of epinephrine caused some reduction in the swelling. During the next two or three days the swelling subsided, but a red blush remained and spread over the cheeks. On October 18 no wheals were left, but where the wheals had been there were sharply defined bright red patches typical of acute lupus erythematosus.

The patient entered the Barnes Hospital for rest and observation. Her past history was unimportant. She apparently had always enjoyed good health except for slight fatigue and malaise which she had noted recently. There was no history of administration of drugs. The results of roentgen examination of the chest were indeterminate. Laboratory examinations gave normal results except for the fact that the leukocyte count varied from 7,500 to 13,800, the Schilling differential count being normal. The temperature was normal. The patient was not actually ill but was not feeling well and had not been well for some weeks.

The patches on the face and arm cleared up rapidly, and after a few days the patient left the hospital. She was put on a regimen of rest; exercise was prohibited, and a high vitamin diet supplemented by ingestion of cod liver oil was prescribed. The patient has gained weight, has felt vigorous and has had no further trouble at the time this report is made. Blood cell counts made in November 1935 and in January 1936 were normal.

Case 2.—H. B., a girl aged 19, was employed as a domestic. She was of a fair, blond type, had pale skin, was of slender build and seemed to be somewhat undernourished. Scattered over the face were pale pink, sharply defined, nearly symmetrical circular patches from 1 to 4 cm. in diameter. The largest was near the center of the forehead. The lobe of each ear was involved, was pinker and more inflamed than the surrounding area and showed slight scaling. These patches had been appearing and disappearing for about two months on all the involved areas except the lobes of the ears, which had exhibited some redness and scaling occasionally for years. There was no history of ingestion of drugs or of any serious illness. During the last year the patient had lost weight, the loss amounting to 5 pounds (2.3 Kg.) or more, and had not been "feeling well," but there had been no definite illness.

She entered the Barnes Hospital for study on Oct. 19, 1935. There were slight fever, the temperature reaching 100 F., and leukocytosis (the leukocytic count was 11,450) with a relative increase in the number of granulocytes. Nothing was found to explain the fever except greatly enlarged tonsils, which, however, showed no inflammation. Physical examination and laboratory examinations gave negative results. Roentgen examination of the chest showed the indeterminate picture of peribronchial infiltration and hilar shadows that are considered practically normal in city dwellers. No evidence of active tuberculosis was observed.

The patient was kept in bed for a few days in the hospital. Her temperature quickly returned to normal, and the leukocyte count decreased from 11,450 to 2,900. The eruption disappeared, leaving a fine scaling. She was discharged from the hospital on Oct. 29, 1935, and given instructions to rest, follow a high vitamin diet and take cod liver oil. In one month she had gained considerable weight, had good color in the skin, felt well and had had no return of the eruption. The leukocyte count was 6,600. Six months later she reported that she was still in good health.

Case 3.—J. F., a married woman aged 31, entered the Barnard Free Skin and Cancer Hospital on Oct. 2, 1935. Two months previously she sustained a

severe sunburn, after which there appeared an acute erythema with fairly definite borders involving the nose and adjacent portions of the cheeks (the butterfly region), the lobes of the ears and the upper lip. This woman was thin to the point of emaciation. She was about 5 feet, 5 inches (65 cm.) tall and weighed 88¼ pounds (40 Kg.). Her husband is a traveling man, and the patient traveled with him; she ate meals at odd hours and followed a rather unbalanced diet, consisting mostly of meat, potatoes and bread. Her general history and the results of physical examination were not noteworthy. There was no history of ingestion of drugs. The patient had never been robust, but, on the other hand, she had never had any definite illnesses. However, two years previously she had become pregnant and had had an induced abortion. After this some fever but no serious illness had been present. A year after she had the first abortion she had again become pregnant and had had another induced abortion. She knew of no trouble having resulted from these abortions. Her menses had been regular and normal. Pelvic examination showed nothing remarkable, with the exception of a slight chronic endometritis and endocervicitis and a mild discharge.

At the time the patient came in the hospital she was feeling generally weaker than usual, had a poor appetite and said she weighed less than she usually did. She was not definite about her usual weight, however. During her stay in the hospital she had a mild pharyngitis with some fever, the temperature reaching about 100 F., which cleared up rapidly. While the fever was present the white blood cell count rose to 11,750. The urine was consistently normal. The patient was in the hospital for about seven weeks. The lupus erythematosus on the face cleared up fairly rapidly, leaving no apparent trace, and she was entirely well when she left the hospital on Nov. 19, 1935, at which time she weighed 107 pounds (48.6 Kg.). The results of laboratory examinations were not significant, with the exception of the low leukocyte count; roentgen examination of the chest showed no evidence of active tuberculosis. The red blood cell count was normal, but the number of leukocytes ranged from 2,250 (on Oct. 1, 1935) to 6,950 (at about the time the patient was discharged from the hospital). The differential blood cell count was usually within normal limits. Up to the time of writing this patient has been entirely well and has felt robust. The treatment has consisted of a high caloric, high vitamin diet and administration of brewer's yeast and cod liver oil. The leukocyte count has remained normal.

Case 4.—H. H., a woman aged 24, was employed as a stenographer. She was blond, had a pale sallow complexion and was rather thin and undernourished. She led an active life, working in the day, missing sleep at night, dancing and joining in social activities. She entered the Barnard Free Skin and Cancer Hospital on April 3, 1935, at which time there was a deep erythema involving the nose, adjacent portions of the cheeks, the upper lip and the lobe of each ear. There were a few small superficial ulcers in the mouth involving the hard palate and the mucous membranes. Also there were symmetrically distributed deep red slightly infiltrated small patches on the dorsum of the distal phalanges of most of the fingers and toes. The eruption had begun on the fingers in November 1934. In January 1935 the red patches appeared on the face and on the toes. The patient had lost some weight, had no appetite and felt weak.

While she was in the hospital she was confined to bed; she was given a high vitamin diet and cod liver oil. Her general history and the results of physical examination revealed nothing remarkable. There was no history of ingestion of drugs. Roentgen examination of the chest showed some infiltrations in the upper lobe of the right lung suggestive of subacute tuberculosis. Five weeks later a roentgenogram showed less mottled infiltration in that area, indi-

cating improvement. The basal metabolic rate was + 11 per cent. The urine contained a few granular casts, and the reaction for the albumin was 1 plus. The Wassermann reaction was negative. Examination of the blood showed 3,820,000 red cells and 60 per cent hemoglobin. The number of white cells was 2,900. The next day the white cells numbered 1,950. The Schilling differential count showed a slight reduction in the number of granulocytes.

Frequent administration of large doses of pentnucleotide resulted in no encouraging rise in the leukocyte count. Two preparations of liver extract were given successively, large doses of each being administered frequently by intramuscular injections given for two weeks. The leukocyte count varied between 2,100 and 4,000, and usually the differential cell count was nearly normal.

On May 25 the patient was reluctantly permitted to go home for a week. Her leukocyte count was only 3,000 at this time, but the cutaneous eruption had nearly cleared up, leaving only a faint trace. She was feeling much stronger and better and had a better appetite. She returned on June 1, complaining that she had "caught a cold." Her throat was bright red, her temperature was 101 F. and she was acutely ill. Her white cell count was 3,175, and examination of the urine disclosed a 2 plus reaction for albumin, red and white blood cells and casts. Acute glomerular nephritis was suspected, and the patient was transferred to the Barnes Hospital on June 3, 1935. There was no recurrence or exacerbation of the patches of lupus erythematosus on the skin of the hands, feet or face during the patient's stay in either hospital. However, a scarlatiniform eruption diagnosed as a toxic erythema appeared over the upper part of the body, lasting only a few days.

In the Barnes Hospital the patient was confined to bed and placed on a regimen of excessive fluid and high carbohydrate intake. Her temperature did not go above 102 F. until three days before death. She complained of lumbar pain, nausea and vomiting. The leukocyte count remained low, ranging from 2,500 to 1,800 until June 9, when it suddenly jumped to 10,400 and showed a marked shift to the left, 8 per cent myelocytes, 12 per cent juvenile forms, 18 per cent stab cells, 48 per cent segmented cells and 14 per cent lymphocytes being present. The next day it fell to 8,850 and the next day to 6,850, and some lessening of the extreme infectious picture was observed. On the morning of June 12, 1935, the patient began to fail rapidly. Her leukocyte count was 3,150; her temperature, 103 F.; her pulse rate, 160 per minute, and her respiratory rate, 45 per minute. Roentgen examination of the chest showed consolidation of the lower lobe of the left lung. The sputum, which had previously contained nonvirulent diphtheroid bacilli and a few staphylococci but no pneumococci, now showed type IV pneumococci, and the same organisms were obtained in cultures from the blood. The patient was given fluids parenterally and a transfusion of 500 cc. of citrated blood, but no improvement resulted, and she died about sixty hours after the onset of pneumonia, as determined by clinical signs and symptoms.

Autopsy.—The autopsy showed lobar pneumonia of the lower lobe of the left lung with fibrinous pleurisy and effusion, pulmonary edema and bronchial pneumonia on the right. There were atelectasis of the upper lobe of the left lung, hydropericardium and fatty degeneration of the liver. There was chronic tuberculosis of the apex of the right lung and the tracheobronchial nodes. The kidneys showed no marked change. The glomeruli were normal. The convoluted tubules were somewhat dilated, and an irregular epithelium and some granular material were present in their lumens. A few contained gray-staining hyaline plugs.

CASE 5.—Mrs. M. J. C., a woman aged 42, was first seen in November 1932. There were slightly scaly noninfiltrated red patches on the forehead, the nose and the adjacent portions of the cheeks. Two years before, a similar spot had appeared on the forehead. Since then, such patches had appeared, remained for varying lengths of time and disappeared. In other respects the general history was not remarkable, and there was no history of ingestion of drugs. The condition was diagnosed as early acute lupus erythematosus, and the patient was told to follow a high vitamin diet and take cod liver oil. A lotion was applied to the face. In a few days an erythema appeared over the forehead, down the sides of the face and over the nose. It was difficult to determine whether the lotion had irritated the skin or whether the erythema represented an exacerbation of the disease. The patient entered the Missouri Baptist Hospital for rest and observation. Roentgen examination of the chest showed an enlarged heart; except for this finding the picture was indeterminate. The leukocyte count varied from 7,000 to 9,900, and there was a slightly lowered granuloctye count. Other studies gave normal results. A few days of rest in the hospital produced such a marked change and improvement in the cutaneous eruption that what was at first a typical acute lupus erythematosus appeared to be a mild, simple dermatitis of no particular character.

CASE 6.—Mrs. E. M. P., a woman aged about 40, had had an eruption over her face for a year and eight months. It would come and go but would remain away only for short periods. Usually a small patch would remain on the nose. She had been treated with many local applications and had undergone numerous intradermal, scratch and patch tests. Nine months before this patient consulted me she was treated with radium for a fibroid tumor of the uterus. The tumor receded as a result of that treatment, and an artificial menopause resulted. There was no history of ingestion of drugs.

When this patient was first seen there was a dermatitis involving the nose, cheeks and forehead, the eruption being rather sharply outlined, especially at the lateral borders. Redness and scaling and, in some areas, crusting were present. A tentative diagnosis of contact dermatitis was made, and the patient was thoroughly studied from that standpoint. She was subjected to patch tests with everything that seemed a likely cause of the eruption. Her environment was changed during her stay in St. Louis from a hotel to an apartment and to a hospital. During this time her eruption spread over the sides of the face and down over the jaws, chin and upper part of the neck. The intensity of the inflammation varied from day to day. Since there was considerable seborrhea of the scalp, a sulfur salve was cautiously tried, but neither improvement nor irritation resulted.

The patient entered St. Luke's Hospital, where it was found that she was fairly normal in most respects; however, the basal metabolism was — 24 per cent. Blood cell counts were normal. Lupus erythematosus of a subacute type had been considered from the first as a possibility, and since dermatitis, either of contact or of seborrheic origin, had been excluded by study and observation of the patient over a period of several weeks, this diagnosis was finally arrived at by elimination. Drs. Engman Sr., Weiss and Bromberg concurred in the diagnosis. The patient was then transferred to the Barnes Hospital, where she was given fever therapy in the Simpson-Kettering cabinet, under the direction of Dr. Leon K. Bromberg. Two treatments were given, and no improvement resulted. After the second episode of fever there was a severe attack of oral herpes. Heat therapy was stopped, since it seemed to upset the patient. During

the last three months the patient has resided in her home city; she has followed a regimen consisting of moderate rest and a high vitamin diet. Improvement has been slow.

To these cases should be added case 2, of the report of Mook, Weiss and Bromberg.[1] I observed this patient also during most of her illness.

She was a well developed girl of great charm, who impressed one particularly by her intense vitality, which made her a fine example of the person who "burns the candle at both ends." The first sign of any trouble was an urticarial type of eruption over the face; this disappeared and later gave place to an erythema involving the cheeks and nose, which indicated the true diagnosis. This rash disappeared as a result of therapy with a gold compound, and the patient remained apparently well for about two years. Then she again had an urticarial type of generalized erythema multiforme. Shortly thereafter a diffuse erythema typical of acute disseminated lupus erythematosus appeared over the face, chest, shoulders and arms. During much of the time this was present the patient had mild fever, malaise and some pain in the chest, which she unwisely concealed from every one. Her course from that time on was progressively toward death. Blood counts early in the course of the disease were not made.

COMMENT

The Patients.—The patients with this condition are in a general way all of the same type. This is particularly noticeable of the young girls. They are overactive, nervously energetic and inclined to indulge in late hours and loss of sleep. Fatigue, with consequent lowering of resistance, is probably an important factor in the development of the disease. The facies in this condition is significant, in that the patient is usually fair or blond, with a pale, sallow skin and pale lips (cases 1, 2, 3, 4 and the case of Mook, Weiss and Bromberg).

The History.—This is usually indefinite in the cases reported in the literature. Probably the important and pertinent facts of the real onset are never brought to light. Case 2 illustrates this possibility. The patient was not at all convinced that anything was wrong with her. The erythematous patches on the face were so evanescent that they might never have prompted her to seek advice. In fact, she had been having similar patches on the lobes of the ears off and on for years and had considered them of no importance. It was at the insistence of her employer that she consulted me. If in such a patient the usual disseminated lupus erythematosus was to develop some time later, the onset would be dated from the time the more severe symptoms began.

The Cutaneous Eruption.—A typical erythema probably is present early in every case. There are definite well defined patches, which are usually distributed over the face, especially over the nose and adjacent portions of the cheeks (butterfly region), though they may appear also in other areas, such as the lobes of the ears, the chest, the back, the shoulders, the arms and the portion of the dorsa of the fingers and

toes just proximal to the nails. There may be symmetrical distribution, but that is not always observed. The patches vary in color from yellowish pink to bright red and are rather definitely outlined. Infiltration is usually slight or absent. Fine scaling occurs when the inflammation begins to subside.

This picture, recognizable as an acute form of lupus erythematosus, may be of short duration, as it was in case 2. It may be recurrent, as it was on the lobes of the ears in that case. Recurrences usually occur in the same site, as they do in fixed drug eruptions. When the eruption first appears it may take an urticarial form, as it did in case 1 and in the case of Mook, Weiss and Bromberg. The erythema may simulate a dermatitis, as in cases 5 and 6, or actual dermatitis may mask the lupus erythematosus if the patient has been using strong local applications. Diagnosis, therefore, may be difficult, and early stages may pass as urticaria, erythema multiforme, seborrheic dermatitis, contact dermatitis or even drug eruption.

No biopsies were made in the cases in this series since the eruption was usually on the face and the patients did not wish to be disfigured.

The Constitutional Symptoms.—In general patients with this condition suffer from mild malaise, loss of appetite and loss of weight to a noticeable but not to a great degree. There may be a mild fever at times. In other words, the constitutional symptoms in cases of early stages of acute lupus erythematosus constitute no specific picture but do indicate lowering of resistance and mild toxemia.

The Leukopenia.—The leukocyte count is of prime importance. In early stages there may be a leukocytosis, as there was in case 1 and 2. As a result of rest the leukocyte count in case 1 returned to normal. In case 2 it dropped to 2,900. Such a drop I consider alarming, but as yet I am unable to interpret it specifically. In case 3 there was a leukocyte count of 2,250, and the number of leukocytes returned to normal after the patient had spent some weeks in the hospital. In case 4 the condition was not in an early stage when the patient was first seen. The cutaneous symptoms were of several months' duration. The leukocyte count was 1,900 on the second day of the patient's stay in the hospital. General treatment and administration of leukopoietic stimulants, such as pentnucleotide and liver extract, did not have much effect. The leukocyte count remained 3,000 or lower. Evidently the leukopoietic system was profoundly depressed in this patient.

The Schilling differential count in the cases in this series was either normal or nearly so, a slight decrease in the number of granulocytes being observed.

In general, the white cell count varies in any particular patient. Early stages are characterized by leukopenia, which may be temporary. A low white cell count that is resistant to treatment is a dangerous

indication. Leukocyte counts should be made repeatedly in any case in which acute lupus erythematosus is suspected. When the diagnosis is established the leukocyte count should be watched for many months after the patient is apparently well.

Resistance to Infection.—Stenn [3] in a recent review mentioned the lowered resistance to infection in patients with agranulocytosis. If one reasons by analogy it is not illogical to assume that in general a markedly lowered leukocyte count may be accompanied by a lowered resistance to infection. Case 4 bears out this assumption. While the patient was in the hospital she was improving greatly as far as her general condition and cutaneous eruption were concerned, but her leukocyte count remained 3,000. She was allowed to go home, where she "caught a cold." This infection of the upper portion of the respiratory tract resulted in exacerbation of the general constitutional symptoms of acute disseminated lupus erythematosus, but the cutaneous eruption did not reappear. The patient died of pneumonia.

E. Schwarz and F. Parkes Weber [4] reported the case of an 11 year old girl who had disseminated lupus erythematosus and whose leukocyte count was 3,800. About six weeks after the onset of the cutaneous symptoms an abscess developed in the lower portion of the right thigh. The patient died shortly after that, apparently of septicemia, although the results of blood cultures were not reported.

Infection, therefore, may be dangerous in that it either may light up the process of acute lupus erythematosus or may of itself cause death in a relatively nonresistant subject.

Treatment.—Since the cause of acute lupus erythematosus is unknown, no specific treatment has been devised. I believe that fatigue has a great deal to do with the production of the disease. The patients are usually active young women who are subjects of chronic fatigue. Rest, therefore, seems indicated as an important therapeutic measure. This means rest in bed when possible. In case 1 exercise was reduced to an absolute minimum for from six months to a year after the patient recovered. Late hours and dancing, with consequent loss of sleep, have been absolutely forbidden in my cases. The patients have been put on a general high vitamin, high caloric diet and given large quantities of cod liver oil. In early stages this regimen seems to produce an immediate response. The appearance, weight and appetite improve. The sense of physical well-being returns. Patients with this condition,

3. Stenn, F.: Etiology of Agranulocytosis, Arch. Path. **20**:902-926 (Dec.) 1935.

4. Schwarz, F., and Weber, F. Parkes: Acute Disseminated Lupus Erythematosus with Staphylococcal Pyemia in a Child, Brit. J. Dermat. **44**:486-489 (Oct.) 1932.

however, should be observed at intervals for many months, as it is often difficult to keep them adhering to a program of this sort when they are feeling well.

SUMMARY

Six cases of early stages of acute lupus erythematosus are reported and discussed to illustrate various points in diagnosis, to stress the importance of early recognition of the disease, to suggest treatment and to advise subsequent observation, especially of the leukocyte count.

ABSTRACT OF DISCUSSION

DR. FRANK C. KNOWLES, Philadelphia: I have tabulated certain figures from certain large dermatologic clinics in Philadelphia, two of which are under the direction of Dr. John Ludy and two of which are associated with my own service. In the last five months my colleagues and I have observed more cases of erythematous lupus than in all of last year. During the last four years the number of cases of the disease has increased by leaps and bounds. The question therefore arises: What is there in the living conditions of persons which may give rise to this acute involvement which may go into the disseminated variety? Is the cause insufficient food, or is it lack of vitamins in the diet? One of the most important points is the extremely low leukocyte count in the patients, particularly in those with rather low fever. Some of our patients have shown a leukocyte count as low as 1,200 and 1,500. Under these circumstances in the cases in which serious constitutional disturbances and marked signs of abdominal symptoms have been present, our first treatment has been blood transfusion. This has been tried in some of the cases, and as a contrast we have carried out the following procedure: As it is known that injections of a gold preparation are frankly contraindicated in cases of acute erythematous lupus, we have obtained blood donors whose blood has been typed. The donors have been given an injection of 100 mg. of a gold preparation. Approximately two hours later 50 cc. of blood from the donor has been injected intravenously in the patients with acute erythematous lupus. Apparently this method has given the best results in cases of acute involvement, and in some instances it has been helpful even when the condition was chronic.

The question arises: What effect could the gold have on certain persons? Could it affect the bone marrow and cause an increase in the number of leukocytes, in that way naturally raising the patient's resistance to the disease?

Another interesting thought, I think, is that of the relationship of the chronic discoid type of the disease to the acute erythematous and disseminated type. In what percentage of cases does the condition change to the acute variety? A number of observers consider that the two types are separate and distinct, and many believe that the discoid type, which is chronic, may change to the acute type.

This is an interesting subject, and I think it would be well for members discussing the paper to give a few figures to show whether the increase in incidence of lupus erythematosus, about 25 per cent of which is of the acute disseminate variety, occurs only in the East, or even only in Philadelphia.

DR. JOHN H. STOKES, Philadelphia: I was interested to hear Dr. Knowles express himmself as he does regarding the increase of acute lupus erythematosus in Philadelphia of late, for I recorded a similar impression before the Phila-

delphia Dermatological Society about a year ago. I think Dr. Engman's effort to unravel early clinical symptomatology is commendable. He observed a group of apparently susceptible young women who lead a life that may predispose to the disease.

In taking careful histories of patients, one is impressed with the inroads of chronic (not acute) fatigue on the constitution of modern men and women. Later and later hours, more and more night life, more and more hurry and exhausting "diversion"—these, together with increasing nervous tension, is, I believe, an important element in predisposing persons to cutaneous disease. Nervous tension is now clearly recognized as an element in the infectious-allergic complexes, and it is possible to make a good case for the classification of lupus erythematosus in this group of diseases. Thus in a way one might suspect a connection between the current enormous incidence of allergic reactions and the inroads of chronic exhaustion. Not only does it seem to me that there is a general spread of the allergic factor in disease, but it appears that certain particular forms of sensitivity are on the increase. Among those is sensitivity to light, a classic element in the lupus erythematosus complex. I have managed to collect a number of instances of apparent predisposing effect of light on susceptibility to pyogenic infection and some cases in which the manifestations suggest a reverse effect. The influence of general and epidemic infection in "stepping up" the allergic susceptibilities is also recognized. In casting about for an allergy-linked infection of general distribution to act as a hypothetic element in the situation one can of course suspect epidemic influenza, the incidence of which, according to reports from the United States Public Health Service, is markedly on the increase and the evil capacity of which as a sensitizer to streptococci was abundantly proved in the epidemic of 1918. It may well be then, it seems to me, that a combination of the fatigue, the allergic and the infectious moments increases the incidence of acute erythematous lupus. This disease, as I have long insisted and as the literature well recognizes, carries in its etiologic complex an allergic type of infection involving the tubercle bacillus. There seems to me, then, ground for regarding acute disseminate lupus erythematosus as an allergic disease, an infection-allergy interplay, chronic exhaustion on the one side and exposure to light on the other being among a number of collateral contributing factors. The highly characteristic and profound leukopenia is an exaggeration of that recognized of late as a manifestation of some forms of allergic shock.

To me these ideas are at least suggestive, and of late my co-workers and I have applied them in our cases of disseminate lupus erythematosus by combating the allergic state, rather than either one, or both, of the suspected infection components. We have prescribed rest and administered autohemotherapy. The results have been good in cases in which the condition was becoming worse in spite of treatment by standard methods. Blood transfusion, as commended by Dr. Knowles, is perhaps a desensitizing procedure, and the function of the minute amount of gold on the blood of the person acting as donor remains, as in the Swift-Ellis intraspinal therapy of neurosyphilis, to be determined.

Dr. Marion B. Sulzberger, New York: I wish to express my pleasure at having had the opportunity to hear Dr. Engman's paper and to emphasize Dr. Stokes' point of view on lupus erythematosus. I think that all dermatologists must come to the conclusion that so-called acute lupus erythematosus is a vascular syndrome which can be produced by a great variety of different agents. I have long believed that to try to find one and the same etiology in all cases of this condition is probably a hopeless search. As soon as dermatologists arrive

at this conclusion and realize that this cutaneous picture may be caused by a multiplicity of factors it will be recognized that the accompanying systemic reactions must also be dependent on various agents. There are many factors, as Dr. Stokes emphasized, which have been incriminated as causes of this picture. One school contends that in many cases the disease is of tuberculous origin. Another group of observers holds that in many cases it is concomitant with streptococcic infections. There are still other cases in which it is accompanied by an abacterial nonverrucous type of endocarditis. I have observed instances in which the clinical manifestations were identical and yet each case represented a different type of etiology. Furthermore, as was brought out, the drop in the number of leukocytes makes one suspect a reaction of hypersensitivity in cases of this disease. And all these considerations suggest that the condition is a syndrome based on a certain form of immunologic response rather than a disease always due to one and the same etiologic factor.

In trying to correlate all these facts and put them together, to combine them all with both the well known hypersensitivity to light and the recently increased incidence of these cutaneous and general reactions, it seems possible that at least in some cases of so-called acute lupus erythematosus the disease may be due to the recent increase in the use of certain drugs or of certain ingredients in food, such as benzoated products and dyes. I think that this aspect merits careful investigation. It is known that the barbiturates can produce vascular damage and purpuric changes and that they can also produce sensitivity to light. It is known that compounds with the benzol nucleus and even certain noncyclic chemicals can produce reductions in the white cells and even agranulocytosis. When all these things are considered one realizes that it would be well worth while to study some of these cases of lupus erythematosus on the basis of at least a careful history as to what drugs (drugs in the widest sense, including chemical adjuvants to foods) have been ingested and to study so-called acute lupus erythematosus carefully from the point of view of possible hypersensitivity to both photosensitizing and leukocytotoxic agents. If one considers that at present many thousands of pounds of these drugs are ingested every year, either in the form of drugs or in that of foods, it becomes evident that this steady increase in drug consumption may well account for the increased incidence of the syndrome known as lupus erythematosus disseminatus acutus.

Dr. Paul A. O'Leary, Rochester, Minn.: I believe the work of my associate, Dr. Welsh, will tend to crystallize the various impressions given by the previous speakers. Several years ago I studied a group of twenty cases of disseminated lupus erythematosus, in half of which autopsies had been made. The lack of evidence of tuberculosis was rather conspicuous in the group, but evidence of an infectious process of some sort was recognized by the pathologist in practically each case in which autopsy was performed. Accordingly, my colleagues and I have made bacteriologic studies in our cases of disseminated lupus erythematosus, and a certain type of streptococcus has been repeatedly isolated by Welsh. This leads me to believe that that organism is the etiologic factor in this disease. The results of this work appear to indicate that chronic discoid lupus erythematosus is not of the same origin as the disseminated type. Exciting or predisposing factors are common in numerous diseases, and it may be that light is one of the several predisposing elements in disseminated lupus erythematosus.

Dr. Isadore Rosen, New York: I am sorry that Dr. Engman did not have sufficient time to give a report of all his cases. I wish to ask whether the five

patients who were dismissed from the hospital are still alive. The results obtained by my co-workers and me have not been as good; most of our patients died.

I have observed most of the cases of lupus erythematosus that have been reported by Dr. Baehr and his associates at the Mount Sinai Hospital. Patients with acute lupus erythematosus who are admitted to the dermatologic service are kept there until the diagnosis is established. Then they are transferred to the medical service because it is felt that the cutaneous manifestations are only a symptom of a systemic disease.

There are one or two points to which I wish to call attention in relation to lupus erythematosus. At present there is a patient at the Mount Sinai Hospital who has been bleeding from the nose and ears for more than two weeks. All attempts to check this bleeding have been futile. She has received three or four transfusions on account of the marked anemia resulting from this constant loss of blood.

Another complication which I wish to mention is bilateral atrophy of the optic nerve due to retinal vascular changes. A case in which that complication occurred was reported by Dr. Isadore Goldstein and Dr. David Wexler (*Arch. Ophth.* **8**:852-856, [Dec.] 1932).

Dr. Paul E. Bechet, New York: Dr. Engman's paper is both practical and interesting. Dr. Stokes mentioned sensitivity to light as being possibly important in the etiology of lupus erythematosus. He also commented on the great increase of cases of that disease in Philadelphia. I have also noted a marked increase in the incidence of the disease in New York, particularly among children of from 2 to 5 years. A considerable majority of the cases occur late in August and in September, and almost invariably there is a history of prolonged exposure to actinic rays. I have often speculated as to the possibility that the wearing of "sun suits" so popular for young children nowadays may be responsible for the increase of the disease among those children. In may opinion, prolonged exposure to actinic rays is not a possible but a definite contributing factor in the causation of both the discoid and the disseminate type of lupus erythematosus. My own experience as well as that of many others has definitely convinced me of that fact. The importance of early diagnosis should be emphasized, for, contrary to the opinion offered by others, I find that therapy with a gold compound, if extreme caution is used, is successful, and the earlier the treatment is given, the better are the results. I do not hesitate to use it in either the localized or the disseminate variety, provided of course, that the latter is not of the fulminating type in which severe constitutional symptoms are present. In cases of that variety therapy with a gold preparation is absolutely contraindicated.

Early stages of lupus erythematosus are often confused with sarcoid or erythema multiforme, but when care is exercised the differential diagnosis is not particularly difficult. Symmetry, infiltration, localization, color and time are the determining factors.

Dr. Richard S. Weiss, St. Louis: I have no statistics that might corroborate the opinion that the incidence of this disease is increasing, but I have the impression that it is. It seems to me that the chief point of Dr. Engman's paper is this: There must be a beginning of lupus erythematosus. Either it is not recognized, or the patient does not come for assistance so early in the course of the disease. When patients of the type described by Dr. Engman are seen by dermatologists, the possibility of disseminate lupus erythematosus should be recognized, and this recognition may in a certain percentage of cases stop the fulminating symptoms that lead to death. In some of the cases reported in this paper the patients have

become clinically well and have remained so for quite a long time. In one of the cases the condition began as an insignificant dermatitis; careful investigation revealed first mild leukopenia; later fulminating symptoms appeared, and the patient died in a few months. Dr. Engman has reviewed a type of disorder in which the beginning of the process is observed and the development of the disease can be followed sometimes to recovery and often to the usual termination. I think the important point is that the paper brings out the fact that hematologically and even clinically one may suspect or recognize the beginning of disseminate lupus erythematosus and by treating the patients with rest and a high caloric and high vitamin diet one may be able in some instances to head off the fulminating symptoms and prevent death.

DR. DUDLEY C. SMITH, University, Va.: I wish to record an objection to the policy mentioned by Dr. Rosen. The transferring of all patients with dermatologic conditions to other services for general management is unwise. Dermatologists should be good practicing internists.

In my opinion, instead of advising a high caloric diet in cases of this condition it would be better to prescribe an abundant diet with a high proportion of proteins and an adequate supply of vitamins. A high caloric diet made up mainly of starches and fats might be deficient in essential factors.

DR. JAMES H. MITCHELL, Chicago: I wish to mention a group of four patients now under my observation. I do not know whether they dance or stay up late at night, but all are in robust health. Two of them have been under observation for three and two years, respectively. They have what might be called acute exacerbations of lupus erythematosus, such as were described by Dr. Engman. These clear without leaving scars, and for want of a better diagnosis I call the eruptions exacerbations of fixed lupus erythematosus. One is of the multiform erythema type; the others consist of flat lesions always occurring in the same area. All the patients are sensitive to light. One is a professional golf instructor. Two have been treated successfully with a gold preparation used cautiously. The other two have just been given their first minute injection of a gold compound and it remains to be seen what will happen. I think that these patients have early stages of acute recurrences of the discoid type. Their condition may later progress to acute lupus erythematosus.

DR. M. F. ENGMAN JR., St. Louis: In regard to Dr. Sulzberger's remarks about drugs, I wish to state that in the cases reported particular attention was paid to the possibility of drugs as an agent, for my co-workers and I have observed some cases in which the leukocyte count was as low as 800 as a result of ingestion of aminopyrine. In none of the cases reported was there a history of ingestion of drugs.

Dr. Rosen asked whether any of the patients died. The one who died (case 4) already had disseminated lesions when she was seen. The leukocyte count was 3,000 and all efforts to get it any higher failed.

Dr. Weiss brought out the important point, namely, that the purpose of this paper is to suggest ways of recognizing the condition earlier than it has been detected. I think that in many cases the acute disseminated type never develops and the disease is not recognized as acute disseminate lupus erythematosus. However, in some cases it is recognized and may be headed off by raising the resistance of the patient.

Dr. Smith spoke of increasing the intake of the proteins. My associates and I precribe what we call a high vitamin diet in cases of furunculosis and other conditions. That diet has a high protein content.

HISTOPATHOLOGY OF VARIOUS TYPES OF CUTANEOUS TUBERCULOSIS

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It is important in cases of obscure manifestations of cutaneous tuberculosis to correlate the histologic with the clinical observations in order to determine the type of cutaneous tuberculosis present and, hence, the prognosis and treatment. The classification given in the table is offered as a working basis, although it is recognized that occasionally more than one form of cutaneous tuberculosis may afflict one patient. The cardinal histologic features of the various types of cutaneous tuberculosis will be emphasized.

Classification of Cutaneous Tuberculosis

Localized Types	Hematogenous Types
Spread by continuity or contiguity of tissues, including secondary lymphatic dissemination	1. Tuberculosis cutis miliaris acuta generalisata
1. Inoculation tuberculosis (including primary cutaneous tuberculous complex)	2. Tuberculosis cutis lichenoides (lichen scrofulosorum)
2. Tuberculosis verrucosa cutis	3. Tuberculosis cutis papulonecrotica
3. Tuberculosis cutis luposa (lupus vulgaris)	4. Tuberculosis cutis follicularis disseminata a. Lupus miliaris disseminatus facei b. Rosacea-like tuberculid (Lewandowsky)
4. Tuberculosis cutis orificialis	5. Tuberculosis cutis indurativa a. Erythema induratum (including nodose types) b. Sarcoid of Boeck (miliary lupoid) c. Sarcoid of Darier and Roussy d. Lupus pernio
5. Tuberculosis cutis colliquativa (scrofuloderma)	

This study is based on a clinical and histologic analysis of about two hundred cases of tuberculosis of the skin observed at the Mayo Clinic. Multiple sections were made and special stains for elastic tissue were used in each case. The classification given in the table, which is essentially that of Gans,[1] was made only after analysis of other classifi-

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1. Gans, Oskar: Histologie der Hautkrankheiten: Die Gewebsveränderungen in der kranken Haut unter Berücksichtigung ihrer Entstehung und ihres Ablaufs, Berlin, Julius Springer, 1928, vol. 2.

cations [2] and correlation of the pathologic observations of Gans,[1] Kyrle,[3] Frieboes [4] and McCarthy.[2a] Space does not permit me to discuss controversial points.[5] The literature on all phases of tuberculosis to 1931 was reviewed by Volk.[2d]

In order to make an accurate histologic classification care must be taken to select for biopsy an old, well developed lesion rather than an early lesion or one that has been subjected to treatment. Fortunately once the type of tuberculosis has become established in a certain case it usually remains the same throughout the course of the disease. Serial sections and elastic tissue stains are often necessary to determine the type of tuberculosis and especially to distinguish hematogenous from localized forms on pathologic grounds alone. It is advisable to obtain material for biopsy deep enough to include the subcutaneous tissues.

Certain general statements regarding the pathology of cutaneous tuberculosis are applicable to all types. In the earliest stages a nonspecific infiltrate composed of polymorphonuclear leukocytes and lymphocytes, with a varying number of tubercle bacilli, can be demonstrated. Within from a few days to a few weeks, according to the type, a specific histologic picture is usually seen. Histologic differentiation of the various types is dependent on the relative degree of caseation necrosis, the number of epithelioid cells and giant cells, the width of the peripheral zone of lymphocytes and plasma cells and the situation and depth of tubercle formation, plus the relationship of the tubercles to blood and lymph vessels. Dissemination through the lymphatic vessels is usual in the localized types but may occur secondarily in the hematogenous types. In all types destruction of elastic tissue is observed where tubercle formation occurs. An active tuberculous focus may exist beneath a scar; frequently it is the result of inadequate treatment. Caseation necrosis in the earliest stages may be dependent on the liquefying action of the polymorphonuclear leukocytes and on the bacilli and their by-products rather than on obliterative changes in lymph or blood vessels. In the older lesions, however, especially in those of hematog-

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2. (*a*) McCarthy, Lee: Histopathology of Skin Diseases: Tuberculosis of the Skin, St. Louis, C. V. Mosby Company, 1931, pp. 239-288. (*b*) Michelson, H. E., and Winer, L. H.: Tuberculodermas of the Face, Arch. Dermat. & Syph. **29**:251-269 (Feb.) 1934. (*c*) Satenstein, D. L.: Tuberculosis of the Skin: Histologic Consideration, ibid. **23**:309-316 (Feb.) 1931. (*d*) Volk, Richard: Tuberkulose der Haut, in Jadassohn, Josef: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 10, pp. 1-686.

3. Kyrle, Josef: Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1927, vol. 2, pp. 161-214.

4. Frieboes, Walter: Grundriss der Histopathologie der Hautkrankheiten, ed. 2, Leipzig, F. C. W. Vogel, 1924, pp. 89-119.

5. Montgomery, Hamilton, in discussion on Michelson, H. E.: Lupus Vulgaris, Arch. Dermat. & Syph. **32**:533 (Sept.) 1935. McCarthy.[2a] Satenstein.[2c]

enous types of tuberculosis, the amount of caesation necrosis seems to coincide with the degree of involvement of the vessels and with their size and depth in the tissues. No emphasis is placed on the presence of mast cells or plasma cells because they are without diagnostic significance. It has not been possible to consider the chemical aspects of the lipoid versus the protein constituents of the tubercle bacillus or to consider the different type of cellular reaction of monocytes, clasmatocytes [6] and other cells which these chemical components call forth in the course of the bodily response. In general, one may state that a marked epithelioid reaction is indicative of a relative resistance of the host or of an attenuated infection, but the presence of a nonspecific lymphocytic infiltrate does not always denote a virulent infection or indicate that one may observe tubercle bacilli. There seems to be no definite relationship between the relative percentage of positive reactions to tuberculin in the various types and their pathologic pictures.

LOCALIZED TYPES

Inoculation Tuberculosis.[7]—This includes the primary cutaneous tuberculous complex.[8] This term should be limited to lesions in the skin exhibited by patients who in the beginning have a negative reaction to tuberculin as well as normal thoracic conditions, as revealed by roentgenograms, and who present no other evidence of systemic tuberculosis; and later—after lymphatic extension of the primary focus—to the cutaneous lesions of patients who have a positive reaction to tuberculin, at times associated with evidence of systemic tuberculosis. The foregoing definition [8b] practically limits the primary cutaneous tuberculous complex to infants and children, because among adults who have inoculation forms of tuberculosis one cannot definitely exclude previous mild, asymptomatic systemic tuberculosis even though the tuberculin test may be negative. The histologic changes in primary cutaneous inoculation tuberculosis run the typical course of a primary infection. During the first few weeks the initial lesion, which clinically

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6. (*a*) Opie, E. L.: Cellular Reactions of Tuberculosis and Their Relation to Immunity and Sensitization, Arch. Path. **14**:706-721 (Nov.) 1932. (*b*) Sabin, F. R., and Doan, C. A.: The Biological Reactions in Rabbits to the Protein and Phosphatide Fraction from the Chemical Analysis of Human Tubercle Bacilli, J. Exper. Med. **46**:645-669 (Oct.) 1927.

7. (*a*) Chancellor, P. S.: Beitrag zur Frage des Primäraffektes bei der Tuberkulose, Ztschr. f. Kinderh. **10**:12-18, 1914. (*b*) Stokes, J. H.: Primary Inoculation Tuberculosis of the Skin with Metastasis to Regional Lymph Nodes, Am. J. M. Sc. **169**:722-736 (May) 1925.

8. (*a*) Bruusgaard, E.: So-Called "Primary Complex" of Tuberculosis in the Skin, Brit. J. Dermat. **46**:113-126 (March) 1934. (*b*) Michelson, H. E.: The Primary Complex of Tuberculosis of the Skin: Review of the Literature, Arch. Dermat. & Syph. **32**:589-601 (Oct.) 1935.

resembles a chancre, a furuncle, an ecthyma or a lesion of sporotrichosis, histologically reveals a nonspecific picture characterized by ulceration, by an infiltrate composed of polymorphonuclear leukocytes, lymphocytes and a few plasma cells and by a varying degree of necrosis. Especially in the areas of necrosis it may be possible to demonstrate numerous tubercle bacilli. Within from three to six weeks after the onset, and at about the same time that there is extension along the lymphatics to adjacent lymph nodes, the histologic picture changes to that of specific tubercle formation with increasing numbers of epithelioid cells and early formation of giant cells; as this occurs the tubercle bacilli become fewer and increasingly difficult to demonstrate. Examination of the adjacent lymph node usually reveals a specific histologic picture, and at this time the tuberculin test also becomes positive. If the primary tuberculous chancre is allowed to progress without treatment or if treatment is inadequate, one may see in from a week to three months after the onset, local lymphatic extension and the development of satellite lesions. These lesions either may have the clinical appearance of the so-called apple jelly nodules of lupus vulgaris or may resemble lesions of tuberculosis verrucosa cutis. Histologically, in its fully developed phase inoculation tuberculosis is characterized by specific tubercle formation with a marked degree of caseation necrosis (fig. 1), the latter distinguishing it from lupus vulgaris. There are numerous giant cells, epithelioid cells and a definite peripheral zone of lymphocytes and plasma cells. Tubercle bacilli can be demonstrated only with difficulty. Extension is along the lymphatic structures.

Inoculation tuberculosis of adults appears in various forms. It may appear as the postmortem wart seen particularly in physicians; it also develops in farmers or veterinarians after abrasions in the skin, possibly from contact with bovine or avian types of tubercle bacilli. It is also seen as an autogenous inoculation of the skin from the patient's own sputum, representing true secondary inoculation. The tuberculous chancre of a patient who has had tuberculosis previously may be nonspecific in clinical and histologic appearance in the first few days. Within an interval much shorter than in cases of the primary tuberculous complex, however, usually in less than a week, the histologic picture is characteristic, and clinically it may be possible to demonstrate apple jelly nodules or the picture of tuberculosis verrucosa cutis. Again, the histologic picture is characterized by specific tubercle formation with marked caseation necrosis. The marked degree of caseation necrosis may in some cases be attributed to bovine rather than to human tuberculosis, but classification as to type of infection was not determined in this series. Simpson [9] has described a rare type of fungating tuber-

9. Simpson, C. A.: Fungating Lymphatic Tuberculosis or Sporotrichial Type of Skin Tuberculosis, South. M. J. **21**:787-791 (Oct.) 1928.

culosis which simulates sporotrichosis and in which numerous ulcers develop up the forearm from the site of the primary inoculation. Stokes [7b] has justly emphasized that in some cases of inoculation tuberculosis the primary lesion undergoes rapid involution; yet often it is possible to demonstrate tubercle formation histologically in the scar tissue.

Tuberculosis Verrucosa Cutis.—In this condition there is a marked verrucous hyperplasia of the epidermis, and underlying abscesses filled with polymorphonuclear leukocytes and lymphocytes are present; usually there are also typical tubercle formation and a moderate amount of

Fig. 1.—Section from lesion of inoculation tuberculosis showing typical picture with marked caseation necrosis.

caseation necrosis in the middle portion of the cutis (fig. 2). At times, however, only a nonspecific reaction can be noted even though many sections are made. The tuberculin test is almost always positive, as it is in all the localized types of tuberculosis. Both clinical or microscopic evidence of lymphatic extension are usually lacking—a feature which distinguishes this condition from inoculation tuberculosis. Blastomycosis is characterized pathologically by double-contoured budding organisms and giant cells, but true tubercle formation is not evident.

Lupus Vulgaris.—Lupus vulgaris presents a varied clinical picture, ranging from that of the typical disorder characterized by apple jelly

nodules to that of fungating verrucous forms or to that of conditions which simulate lupus erythematosus. The histologic picture, however, is characterized by typical tubercle formation with epithelioid cells, giant cells and a definite peripheral zone of lymphocytes. Little, if any, caseation necrosis is present. Histologically lupus vulgaris can be divided according to whether tubercle formation is diffuse or discrete. The diffuse type is usually the result of secondary lymphatic dissemination. Occasionally one encounters secondary changes in the epidermis which vary from thinning of the epidermis through pressure atrophy to verru-

Fig. 2.—Section from lesion of tuberculosis verrucosa cutis showing verrucous hyperplasia of epidermis with abscesses beneath, definite tubercle formation with giant cells and early caseation in the middle portion of the cutis.

cous hyperplastic changes; the latter changes may develop even to the extent of forming pseudo-epitheliomatous hyperplasia. In chronic indolent types one may sometimes observe almost pure epithelioid tubercles which simulate the histologic picture of sarcoid, although the tubercles lack the hematogenous distribution characteristic of sarcoid. Lupus vulgaris is essentially inoculation tuberculosis, the inoculation taking place either within or without, from sputum. Hence, in some cases lupus vulgaris occurs in association with tuberculosis of the mucous membrane. New capillaries may form as a result of the tuberculous granuloma. Occasionally the walls of a blood vessel are eroded,

thus permitting hematogenous spread of the disease. Tubercle bacilli may be demonstrated in the tissue in cases of lupus vulgaris but only, as a rule, with difficulty.

Tuberculosis Cutis Orificialis.—The histologic picture of tuberculosis of the mucous membranes is often nonspecific, as is the clinical picture. The latter may be characterized by ill defined multiple ulcers, grayish plaques or marked verrucous changes and lymphedema where the lymphatic channels have been obstructed. Histologically, varying numbers of bacilli are demonstrable in the cutis; this is indicative of lack of resistance or of a more virulent infection and hence justifies a more serious prognosis. Manifestations of systemic tuberculosis are usually present. The verrucous changes in the epidermis may simulate epithelioma,[10] and the pathologic picture of a gumma may be imitated. Specific tubercle formation, seen especially in the more chronic forms, may simulate the histologic picture of lupus vulgaris or tuberculosis verrucosa cutis.

Scrofuloderma.[11]—Tuberculosis cutis colliquativa represents direct or lymphatic extension to the skin from an underlying tuberculous focus, such as may be present in the lymph nodes or in bone. Sinuses and ulceration result. The histologic picture in the center of the abscess, or at the margin of the sinus, may be nonspecific, but in the deeper portions of the lesion and at the periphery one usually sees specific tubercle formation consisting of marked caseation necrosis and the presence of epithelioid cells, giant cells and many lymphocytes. The presence of many plasma cells may at times cause the picture to simulate that of syphilis. Tubercle bacilli may occasionally by demonstrated. Occasionally, at the margins of the sinus, typical apple jelly nodules and the histologic picture of lupus vulgaris develop.

HEMATOGENOUS TYPES

Tuberculosis Cutis Miliaris Acuta Generalisata.—This type represents acute fulminating miliary tuberculosis of children and is encountered in two forms.[12] The first form is the result of cutaneous dissemination of pulmonary or meningeal tuberculosis, while the second

10. Morrow, Howard, and Miller, H. E.: Tuberculosis of the Tongue, J. A. M. A. **83**:1483-1487 (Nov. 8) 1924.

11. Michelson, H. E.: Scrofuloderma Gummosa (Tuberculosis Colliquativa), Arch. Dermat. & Syph. **10**:565-578 (Nov.) 1924. Volk.[2d]

12. Funk, C. F., quoted by Wise, Fred, in The 1934 Yearbook of Dermatology and Syphilology, Chicago, The Year Book Publishers. Inc., 1934, pp. 329-338. Geipel, P.: Die Beteiligung der Haut bei Miliartuberkulose, Virchows Arch. f. path. Anat. **286**:591-603, 1932. Tileston, Wilder: Disseminated Miliary Tuberculosis of the Skin: An Important Sign in General Miliary Tuberculosis of Infancy, Arch. Int. Med. **4**:21-31 (July) 1909.

form appears after the exanthematous diseases or some severe infection. In the latter form one may see the numerous discrete papulovesicular hemorrhagic crusted lesions become chronic and take on features characteristic of lupus vulgaris, or occasionally they may be observed to undergo spontaneous involution. Histologically, little evidence of reaction is observed in the cutis except dilated blood vessels packed with tubercle bacilli; also tubercle bacilli are found lying free in a zone of necrosis about the blood vessels. If the disease is more chronic there may be an inflammatory reaction of lymphocytes about the blood vessels, and later even definite tubercle formation.

Tuberculosis Cutis Lichenoides (Lichen Scrofulosorum).—This is a benign type of hematogenous tuberculosis seen most frequently in children but occurring also in adults. It is characterized by small grouped lichenoid or follicular noninflammatory papules. The histologic picture is that of an infiltrate, superficial as a rule, limited to the hair follicles or sweat ducts, but occasionally independent of either, and most frequently specific. The infiltrate consists of almost pure epithelioid tubercles, an occasional giant cell and a narrow zone of lymphocytes at the periphery of the tubercles. The localization to hair follicles is accounted for by their rich vascular supply [13] and by the fact that in this type the finer and smaller blood vessels are involved. It is interesting that in Rauschkolb's [14] series more than 50 per cent of the patients also had phlyctenular conjunctivitis. There is no caseation or change of the subcutaneous tissues.

Tuberculosis Cutis Papulonecrotica.—Under this term are included the papulonecrotic lesions that develop on the trunk or extremities as well as those that appear on the face, in which case the condition is designated as acnitis, and those that appear on the hands, in which case the condition is known as folliclis. The pathologic picture (fig. 3) is that of hematogenous tuberculosis involving the blood vessels in the middle and deeper portions of the cutis; the result usually is obliterative endarteritis and endophlebitis with thrombosis and recanalization of the lumens of the vessels; hence the development on the skin of necrotic crusted ulcers. One usually encounters specific tubercle formation with a moderate amount of caseation necrosis and also some Wucher atrophy of the subcutaneous tissue (fat replacement atrophy).

Tuberculosis Cutis Follicularis Disseminata.—This condition is a much debated one and is known by a multiplicity of names. The term lupus miliaris disseminatus faciei is confusing, for the condition is

13. Wise, Fred: Miliary Tuberculosis of the Skin, Lichen Scrofulosorum and the Papulo-Tuberculids, J. Cutan. Dis. **37**:105-124 (Feb.) 1919.

14. Rauschkolb, J. E.: Tuberculosis of the Skin: A Clinical Report, Arch. Dermat. & Syph. **29**:398-407 (March) 1934.

different from lupus vulgaris. In tuberculosis cutis follicularis disseminata the miliary, discrete nodules are as a rule limited to the face. The histologic picture is characterized by specific tubercle formation centered about the blood vessels, many of which have undergone obliterative changes resulting in caseation necrosis (fig. 4). Destruction of the hair follicles and sebaceous glands occurs. The few cases of a fine papular eruption of tuberculosis affecting Negroes which I have

Fig. 3.—Section from lesion of tuberculosis cutis papulonecrotica stained with elastin H stain showing tubercle formation in the cutis and subcutaneous tissue centered about an obliterated blood vessel; also, fat replacement atrophy.

observed would, I believe, best be placed in this group, along with Wise's and Satenstein's cases,[15] rather than with cases of sarcoid,[16] chiefly because of the definite caseation necrosis seen histologically.

15. Wise, Fred, and Satenstein, D. L.: Clinical and Histologic Features of Certain Types of Cutaneous Tuberculosis, Arch. Dermat. & Syph. **4**:586-608 (Nov.) 1921.

16. Nomland, Ruben: Hematogenous Cutaneous Tuberculosis (Sarcoid) in Negroes: Report of Six Cases, Arch. Dermat. & Syph. **30**:59-75 (July) 1934.

As a subdivision of tuberculosis cutis follicularis disseminata I have listed the rosacea-like tuberculid of Lewandowsky because of its similar distribution. The clinical picture recently has been emphasized by Wile and Grauer [17] and by MacKee and Sulzberger.[18] Histologically, nonspecific and specific tubercle formation are observed centered about blood vessels in the upper portion of the cutis. Usually almost pure epithelioid tubercles are observed about the hair follicles, but there is no destruction of the sebaceous glands or invasion of the deeper portions of the cutis. There is dilatation of the capillaries in the papillary bodies,

Fig. 4.—Section from lesion of tuberculosis cutis follicularis disseminatus showing definite tubercle formation with marked caseation necrosis. *C*, the result of an obliterated blood vessel, *bv*.

which contributes to the rosacea-like appearance. There is no caseation necrosis, a feature in which the condition differs from lupus miliaris disseminatus.

17. Wile, U. J., and Grauer, F. H.: Rosacea-Like Tuberculosis: Review of the Literature with Report of Five Cases, Arch. Dermat. & Syph. **31**:174-189 (Feb.) 1935.

18. MacKee, G. M., and Sulzberger, M. B.: Rosacea-Like Tuberculid of Lewandowsky, Arch. Dermat. & Syph. **31**:159-173 (Feb.) 1935.

Tuberculosis Cutis Indurativa.—This condition, both from the histologic and clinical point of view, has been divided, it seems to me unnecessarily, into a multiplicity of types. This subdivision is unwarranted because frequently two or more forms are observed in the same patient.[19] Erythema induratum, which is similar to, but more severe than, papulonecrotic tuberculid, is characterized by involvement of the larger and deeper vessels in the subcutaneous tissue, and obliterative changes result, as a rule, in secondary ulceration of the epidermis. The following changes also are observed: specific tubercle formation with definite caseation necrosis, epithelioid cells, giant cells, a peripheral zone of lymphocytes and a marked degree of Wucher atrophy as a result of specific and nonspecific infiltration of the subcutaneous tissue. At times one encounters clinically a nodose and nonulcerating type, development of which is dependent on the extent and the degree of the involvement of the blood vessels. This nodose type, under the heading of which Wende's tuberculosis of the hypoderm may be included, usually can be distinguished from erythema nodosum of streptococcic or rheumatic origin by its different symptomatology [20] and greater chronicity as well as by different pathologic characteristics.

Sarcoid of Boeck.—This condition may appear either as the small multiple nodular (miliary lupoid) type or as the plaque type. Darier [21] also included the angioid lupoid of Pautrier, which he regarded as sarcoid of Boeck with dilated vessels. Kyrle [3] has demonstrated histologically in sarcoids of a few days' duration a nonspecific perivascular lymphocytic infiltrate with numerous tubercle bacilli. Within a few weeks, however, the picture changes to that of epithelioid tubercles, and bacilli are no longer demonstrable. Sarcoid of Boeck is characterized by almost pure epithelioid tubercles centered about blood vessels throughout the upper and the middle portion of the cutis. There are few giant cells, and a very narrow zone of lymphocytes surrounds the tubercle. There is little or no caseation necrosis. At times a nonspecific histopathologic picture may be encountered.

Sarcoid of Darier and Roussy.—This is distinguished from the Boeck type of sarcoid in that the Darier-Roussy type is as a rule localized to the trunk and extremities and by the fact that in this dis-

19. (*a*) Finnerud, C. W.: A Clinical, Histologic and Bacteriologic Study of a Case of Multiple Benign Sarcoid of Boeck-Darier-Roussy, Arch. Dermat. & Syph. **4**:342-352 (Sept.) 1921. (*b*) Goeckerman, W. H.: Sarcoids and Related Lesions: Report of Seventeen Cases; Review of Recent Literature, ibid. **18**:237-262 (Aug.) 1928. (*c*) Maloney, E. R., and Combes, F. C.: Darier-Roussy Sarcoid with Special Reference to Its Tuberculous Etiology, ibid. **33**:709-724 (April) 1936.

20. Stokes, J. H.: Clinical Studies in Cutaneous Aspects of Tuberculosis: I. "Tuberculous" Purpura, Erythema Multiforme and Erythema Nodosum, Am. J. M. Sc. **157**:157-170 (Feb.) 1919.

21. Darier, Jean: Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928.

order epithelioid tubercle formation usually begins in the middle portion of the cutis and subcutaneous tissue. Some caseation necrosis may also be seen. A nontuberculous epithelioid reaction [19c] can be distinguished histologically, I believe, by careful analysis of concomitant changes.

Lupus Pernio.—This form (fig. 5) differs from sarcoid of Boeck only in the marked dilatation of the superficial capillaries. Again, in lupus pernio, there is epithelioid tubercle formation around blood vessels. In all forms of sarcoid, roentgenograms frequently reveal fibrocystic changes in the terminal phalanges and infiltration of the lungs. Because of positive anergy the tuberculin test is most frequently negative in all cases of sarcoid, including cases of lupus pernio.[22]

Many rare forms of tuberculosis are reported, representing such conditions as hematogenous types of scrofuloderma,[23] tuberculid en plaques,[24] exfoliative dermatitis (pityriasis rubra of Hebra attributable

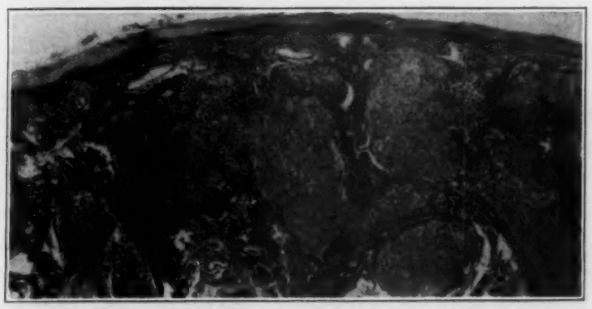

Fig. 5.—Section from lesion of lupus pernio showing dilated capillaries and almost pure epithelioid tubercle formation.

to tuberculosis),[25] certain types of lividoracemosa,[26] generalized telangiectasia [27] and poikiloderma of Jacobi, as well as tuberculous paronychia [28]

22. Sulzberger, Marion B.: Sarcoid of Boeck (Benign Miliary Lupoid) and Tuberculin Anergy, Am. Rev. Tuberc. **28**:734-745 (Dec.) 1933.

23. Montgomery, Hamilton: Unusual Cutaneous Tuberculosis (Hematogenous in Type) Proved by Demonstration of Bacilli of Tuberculosis in the Skin, M. Clin. North America **19**:611-618 (Sept.) 1935.

24. Sweitzer, S. E.: Tuberculide en Plaque, Arch. Dermat. & Syph. **24**:842-852 (Nov.) 1931.

25. Barney, R. E.: Pityriasis Rubra (Hebra), Arch. Dermat. & Syph. **18**:716-729 (Nov.) 1928.

26. Ebert, M. H.: Livedo Reticularis, Arch. Dermat. & Syph. **16**:426-441 (Oct.) 1927.

27. Becker, S. W.: Generalized Telangiectasia: A Clinical Study, with Special Consideration of Etiology and Pathology, Arch. Dermat. & Syph. **14**:387-426 (Oct.) 1926.

28. Stokes, J. H.: Tuberculous Paronychia: Report of a Case with Unusual Features, Arch. Dermat. & Syph. **8**:44-47 (July) 1923.

and also variants of the classification given in the table. Correlation of clinical and histologic observations is often of value in classifying these conditions and in determining the prognosis and treatment.

CONDITIONS ALLIED TO TUBERCULOSIS

Many conditions the etiology of which remains to be proved have been considered to be tuberculosis. Lichen nitidus bears the closest resemblance to tuberculosis in that there is frequently an epithelioid tubercle formation, especially about the sweat ducts, and occasionally even giant cells are present. The presence of giant cells raises the question of confusion clinically and histologically with lichen scrofulosorum. There is lack of concomitant evidence of tuberculous etiology. The tuberculous etiology of granuloma annulare is still a matter of debate.[29] The histologic picture, however, is that of a central area of coagulation necrosis of the connective tissue and a peripheral zone of lymphocytes, connective tissue cells, polymorphonuclear leukocytes and a few epithelioid cells. There is no evidence of true tubercle formation. Whereas Dietrich reported that he demonstrated tubercle bacilli in cases of granuloma annulare, the technic he used has since been questioned. Erythema elevatum diutinum presents a distinctive histologic picture.[30] Ramel and others would include both erythema multiforme and erythema nodosum under tuberculosis. The histologic picture has nothing to suggest tuberculosis, if one excludes those cases of the nodose type of erythema induratum which has been erroneously diagnosed as tuberculosis.

Disseminate forms of lupus erythematosus are not uncommonly associated with tuberculosis or streptococcic infection of the internal organs; yet histologically there is not any pathologic change indicative of tuberculosis and tubercle bacilli are not demonstrated in the skin.[31] The occasional instances in which lesions of lupus erythematosus and of various tuberculids are seen in the same patient do not necessarily imply a common etiology. Pernio (chilblain) is mentioned only because of the fact that it is sometimes confused with lupus pernio.

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29. Michael, J. C.: Etiology of Granuloma Annulare with Special Reference to the Tuberculous Theory, Arch. Dermat. & Syph. **29**:189-205 (Feb.) 1934.

30. Weidman, F. D., and Besancon, J. H.: Erythema Elevatum Diutinum: Rôle of Streptococci, and Relationship to Other Rheumatic Dermatoses, Arch. Dermat. & Syph. **20**:593-620 (Nov.) 1929.

31. Goeckerman, W. H., and Montgomery, Hamilton: Lupus Erythematosus: An Evaluation of Histopathologic Examination, Arch. Dermat. & Syph. **25**:304-314 (Feb.) 1932. Keil, Harry: Relationship Between Lupus Erythematosus and Tuberculosis: A Critical Review Based on Observations at Necropsy, ibid. **28**: 765-779 (Dec.) 1933.

TUBERCULOID REACTIONS

Tuberculoid reactions are not uncommon in cases of acute syphilis of the lymph nodes; occasionally, they appear in cases of secondary and tertiary cutaneous syphiloderma (fig. 6). Syphilitic changes about the blood vessels at the periphery of the lesion usually permit proper diagnosis. The anergic tuberculoid type of leprosy, characterized by epithelioid tubercles, usually is accompanied by changes in the cutaneous nerves. Foreign body reactions attributable to paraffinoma, to improper

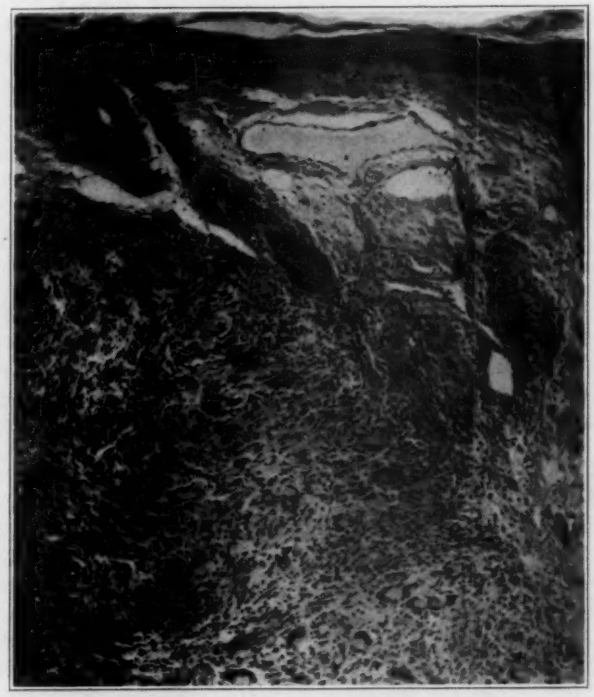

Fig. 6.—Section from tertiary syphiloderm showing tuberculoid reaction; endarteritis and syphilitic vascular changes are present at the periphery of the nodule.

injection of various drugs and to ingrowing hairs are distinguished from tuberculosis by the presence of foreign body giant cells (which differ from Langhans giant cells in their clumping and irregular arrangement of nuclei) and by the absence of true tubercle formation. Foreign body giant cells may also be seen in tuberculous lesions, however, often because of involvement and invagination of hair follicles.

SUMMARY AND CONCLUSIONS

The various forms of tuberculosis of the skin can be grouped under localized and hematogenous types. A fairly accurate classification based on histologic observations alone is usually possible because the various types of cutaneous tuberculosis tend to persist as such. The cardinal histologic changes in the various types are known, as well as the features which distinguish one from another. The histologic differentiation of the various types is dependent on evaluation of the relative degree of caseation necrosis, on the presence of epithelioid cells, giant cells and a peripheral zone of lymphocytes and plasma cells, on the situation and depth of the tubercle formation and on the relation of such tubercles to blood vessels. It is important to make a careful selection of the lesion from which material is to be taken for biopsy, and in many cases it is necessary to make serial sections and to stain for elastic tissue. Correlation of the clinical and histologic observations is especially valuable in obscure cases in order to determine the type of cutaneous tuberculosis present and hence indicate the prognosis and treatment. The type of pathologic response, varying from a nonspecific one with many bacilli to the picture of epithelioid tubercle formation, may be of value in prognosis and treatment. It is necessary to differentiate tuberculous cutaneous reactions from other diseases, including conditions allied to tuberculosis and conditions which cause tuberculoid pathologic reactions.

ABSTRACT OF DISCUSSION

Dr. Duncan O. Poth, San Antonio, Texas: There are several points that may be emphasized in this discussion. The care that should be taken in the selection of the site from which material biopsy is to be taken has been pointed out. It is important to make biopsies not only in cases of cutaneous tuberculosis in which the picture is not clearcut, but in cases of almost any dermatosis in which the condition is obscure. This fact is illustrated in a recent article by Riordan in which he stated that biopsies revealed cutaneous tuberculosis in instances in which a condition had been clinically diagnosed as epithelioma, Hodgkin's disease or keloidal acne.

I feel that Dr. Montgomery's article offers the solution to the error that may persist in private practice. As many as two hundred and fifty sections have been studied in one single biopsy. I was also told that it was not uncommon to examine as many as twenty-five serial sections before the typical tuberculoid structure was found. Obviously, if after a biopsy is made and one or two sections are prepared, stained and examined the correct tuberculous structure is not observed, the error is plain.

Dr. Montgomery is to be commended for having presented a workable classification of cutaneous tuberculosis. It seems plausible that such a classification should be accepted, because it is based on accurate histologic observations. It was likewise pointed out that the various forms of cutaneous tuberculosis tend to persist as such.

This discussion represents a tremendous amount of work. Some two hundred cases of cutaneous tuberculosis have been thoroughly studied, and the observations have been interestingly presented.

Dr. Marion B. Sulzberger, New York: Dr. Montgomery's paper is timely because recently dermatologists have been more interested in cutaneous tuberculosis than in preceding years, as is shown by the plethora of recent articles on this subject. This interest has not always led to valuable or sound contributions. Recent articles have tended to increase confusion rather than to bring clarity, and I hope that Dr. Montgomery's paper will help to clarify many points. This paper is also timely because the general pathologists and immunologists have again shown a recrudescence of their interest in tuberculoid structures and in the causes of tuberculoid structures. This is shown, for example, by the chemical analyses of the tubercle bacilli, by the newer different types of tuberculin and by the studies of these chemical fractions as to their propensity for producing different types of tissue reactions, i. e., one fraction being regarded as producing the necrosis and another fraction as producing the tuberculoid structure.

Dr. Montgomery's presentation does not pretend to set forth a new or original classification. It is a replica of the classification established by Jadassohn and Lewandowsky and their schools. Dr. Montgomery presents it as such. It is high time that this matter be clearly presented, for, unfortunately there is no such clear compilation in the American literature.

Another interesting point of view to set forth would be the attempt not only to correlate the histologic and the clinical picture but also to demonstrate the tubercle bacilli in the varying and different histologic and clinical forms by means of inoculations of guinea-pigs. A further consideration would be (and I hope Dr. Montgomery will be able to carry on his work in this direction) to correlate the histologic and clinical picture with the presence of bacilli, and all these observations in turn with the reactions to quantitative tests with tuberculin. One of the interesting aspects of the whole problem is that the type of response to tuberculin is a relative indication of the type of histologic response and that both of these, to some degree, determine the clinical picture, the course of the disease, the prognosis and the manner in which the disorder will react to therapy.

From this classification one can clearly see that it has been possible to differentiate histologically between forms of cutaneous tuberculosis associated with marked hypersensitivity to tuberculin, forms of cutaneous tuberculosis associated with a sensitivity to tuberculin approximating the normal and forms of cutaneous tuberculosis associated with a sensitivity to tuberculin less than that exhibited by normal persons without tuberculosis of the skin. I hope that Dr. Montgomery will be able to carry on work in regard to the correlation of histologic and immunologic vagaries in individual cases of all tuberculoderms; i. e., that he will determine, for example, whether a histologically aberrant form of lupus miliaris produces an aberrant reaction to tuberculin, if lupus vulgaris with a peculiar histologic picture is associated also with a peculiar response to tuberculin. This would prove an interesting and useful study and should contribute something new to the understanding of the importance of immunologic factors in the morphology and course of tuberculoderms.

Dr. Richard L. Sutton Jr., Kansas City, Mo.: A discussion of the pathology of cutaneous tuberculosis is scarcely complete without mention of the work which Florence Sabin did with intracutaneous injection of various fractions of tubercle bacteria, the chemical fractions being purified and inoculated separately.

It is the waxy and phospholipid fractions which evoke the epithelioid cell response. It is the protein fraction that evokes the hemorrhagic and necrosing

and lymphocytic response. The other fractions have been similarly tested, and responses to them have been carefully and accurately reported.

The histologic picture produced in the skin must depend accurately on the number and activity of the bacteria present, on their state of activity and on their chemical composition at the site where they produce the lesion. If their presence cannot be demonstrated histologically or by inoculation of animals, they must be dead and present in the form of chemical products.

Dr. Montgomery's classification is eminently workable and is not greatly different from the one given in the latest edition of "Diseases of the Skin" by Sutton and Sutton.

Dr. C. W. Finnerud, Chicago: Dr. Montgomery's demonstration emphasizes the diminishing number of entities which were formerly classified as tuberculids and were understood to be manifestations of the toxins of the organism, the latter acting from a distant focus. One of the most important features of his paper is the fact that he has shown that if material for biopsy is taken from well developed lesions and excised deeply enough, and if a sufficient number of sections is made, either serially or at least from different parts of the block, the most characteristic structure will be observed and the picture will be fairly definite. Personally, however, I do not feel that one can always, or even often, accurately determine from histologic observations alone the type of tuberculous lesion which is present.

I wish to ask Dr. Montgomery to stress what he now considers to be a tuberculid, a lesion due to the toxins of the organism rather than to its local action, since it is now known that many, if not all, the clinical entities related to this group which were previously considered to be an id eruption, such as sarcoid, are really due to the local action of the organism, even though the organism was early destroyed by the existing allergic state.

Dr. Herbert S. Alden, Atlanta, Ga.: This paper impressed on me the added importance of the biopsy in cases of tuberculosis and tuberculids. Many eruptions of this kind are exhibited by Negro patients in Atlanta, Ga., and in most cases the disorder cannot be clinically diagnosed more accurately than as tuberculid. Sections are always reported by general pathologists to show sarcoid, without differentiation as to the type of sarcoid. I certainly appreciate the classification given by Dr. Montgomery. I think one should be more intent on making biopsies in cases of such disorders.

Dr. Donald M. Pillsbury, Philadelphia: In connection with this extraordinarily complete presentation of Dr. Montgomery's, I wish to mention one type of disorder which he did not have time to mention but which he has included in his exhibit, namely, tuberculous purpura.

I should like to record a case which I recently observed in the medical service of the Temple University Hospital, because it presented several interesting features. In a man aged 67 there developed suddenly, after a griplike illness of two weeks' duration, severe purpura with hemorrhage from the bowels and from the nose and profound thrombopenia, the platelet count never exceeding 17,000. There was evidence of old tuberculosis in both lungs, and because of this and of the lack of any other probable etiologic factor, it was suggested that the purpura might be tuberculous. At autopsy, generalized miliary tuberculosis was observed.

An interesting feature in the case was that the patient was also apparently radiosensitive. As a result of irradiation of the spleen with doses which would cause no cutaneous reaction in a normal person, there developed a slightly purpuric papular dermatitis, both anteriorly and posteriorly over the region of the spleen.

I think that internists in general do not recognize that in some cases purpura may be tuberculous. One has been accustomed to regard this condition as occurring particularly in infants and in young adults, but age is not, apparently, an absolute criterion.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Regarding the chemical factors, I wish to say that in none of the cases were studies made with relation to the work of Sabin and Doan and others concerning the protein and lipoid contents of the lesions and their various responses. In cases of the benign hematogenous types of tuberculosis, I believe the caseation necrosis is dependent chiefly on the degree of obliterative changes of the blood vessels and their location and size; this is in contrast to inoculation tuberculosis, for example, in which there is a primary infection with the direct effects of the bacilli and their by-products and in which in the early stages leukocytosis is present—all of which contribute to the caseation necrosis.

I purposely avoided the use of the term tuberculid, because it has been misused and it is difficult to define it satisfactorily for every one. Most of the hematogenous types of tuberculosis, including sarcoid, have been proved definitely to be true tuberculosis and not ids in the older sense of a toxic process.

Regarding tuberculosis in Negroes, I have not had enough experience to classify the group that is being discussed by the eastern dermatologic societies; namely, the combination of sarcoid and lupus miliaris disseminatus. I think that probably the disorder belongs with lupus miliaris disseminatus rather than with sarcoid, because histologically there is marked caseation necrosis, a feature which is not present in sarcoid.

I want to emphasize that it is important to have the senior dermatologists in a group select an area from which material for biopsy is to be taken; the selection should not be left to one of the students. A general pathologist at postmortem examination in looking for an obscure tuberculosis of the lung carefully selects the site from which the specimen for biopsy is to be taken and does not leave that task to his assistant or to a student.

Minor Notes

CERVICAL RIBS (?)

FRED D. WEIDMAN, M.D., PHILADELPHIA

Within the last few months I have had two experiences with disturbances of the skin which have been associated with cervical ribs. One was a congenital trophic ulcer of the fingers in a child aged 6 years. The second was a dermatitis of the hand. The circumstance that attracted attention to a possible neurologic (pressure) factor was the unilaterality of the involvement in each case, and, in addition, a distribution that was not consistent with that of any of the commoner dermatoses. I saw the patients in consultation and, unfortunately, I was not able to influence decision as to rational (surgical) therapy.

My attention was called to the possibility of cervical ribs as a factor in inducing dermatoses by an article published twenty or thirty years ago in which Dr. Wayne Babcock reported a small series of cases of Raynaud's disease in some of which improvement followed surgical removal of such ribs.

My object in reciting these two experiences is to attract the attention of dermatologists to the possibility of cervical ribs in cases of unilateral, and conceivably also of bilateral, disorders consisting of lesions which appear to be trophic, occur on the upper extremities and are not explainable by ordinary causes.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

PYOGENIC SKIN LESIONS ACCOMPANYING CHRONIC ULCERATIVE COLITIS. I. R. JANKELSON and B. F. MASSELL, Am. J. Digest. Dis. & Nutrition **3**:19, 1936.

Cutaneous lesions in the course of ulcerative colitis occur during the active stages of the primary disease and assume a great variety of forms. The lesions vary from recurrent crops of blebs to punched-out ulcerations, pustular cutaneous lesions and multiple abscesses. These abscesses may break down and slough, leaving large ulcerating areas. The lesions may be metastatic or may be due to secondary invasion of the skin during lowered resistance. The organisms cultured were Staphylococcus aureus, Staphylococcus albus and hemolytic streptococci, the various organisms occurring either separately or together.

The treatment is primarily that for ulcerative colitis.

AUTHORS' ABSTRACT.

ON THE EXISTENCE OF AN INTRINSIC DEFICIENCY IN PELLAGRA: A PRELIMINARY REPORT. V. P. SYDENSTRICKER, E. S. ARMSTRONG, C. J. DERRICK and P. S. KEMP, Am. J. M. Sc. **192**:1 (July) 1936.

Sydenstricker and his associates administered gastric juice in varying amounts to six pellagrins over periods of from ten to forty-nine days. Five of the six patients were kept on a pellagra-producing diet.

In several patients improvement was far more rapid than would have been anticipated even with an optimum diet reenforced with vitamin B_2.

In commenting on the results of their experiments the authors suggest the possibility of an intrinsic factor in the gastric juice which promotes a rapid recovery by utilization of minimal amounts of extrinsic factor (B_2).

They feel that in pellagra there is a variable degree of deficiency of intrinsic factor, some patients retaining enough, however, to recover even on diets deficient in vitamin B_2. Others may rapidly regenerate this factor, while in still others it may be totally lacking.

Prolonged deprivation of extrinsic factor may result in complete exhaustion or inability to regenerate the intrinsic factor.

THE ADVANTAGES OF VACUUM DRIED COMPLEMENT FOR USE IN THE ROUTINE WASSERMANN REACTION. F. BOERNER and M. LUKENS, Am. J. M. Sc. **192**:272 (Aug.) 1936.

After using vacuum-dried complement in performing several thousand Wassermann tests of the blood and spinal fluid Boerner and Lukens expressed the belief that this complement is fully equivalent to fresh complement.

The complement, dehydrated from the frozen state, sealed in vacuo and stored at from 8 to 10 C., was found to retain its full hemolytic activity and fixability for a period of twelve months. After that time it deteriorated.

JAMIESON, Detroit.

DERMATOMYOSITIS. A. WOLF and S. L. WILENS, Am. J. Path. **12**:235, 1936.

Dermatomyositis is an inflammatory, often degenerative, disease of the skin and striated musculature. The cutaneous reaction resembles erythema, erythema nodosum, erythema multiforme, erysipeloid, roseola or urticaria; a nonpitting edema develops and then scaling, and the involved tissues become brownish, leathery, tight, atrophic and fixed to the underlying tissues, the process often ending in scleroderma. The papillae are flattened, the cells of the basal layer vacuolated, the

dermis edematous and its collagen fibers swollen and semihyaline. Perivascular and periglandular infiltration by round cells occurs, chiefly lymphocytes and monocytes collecting, especially beneath the epidermis. Finally, desquamation of the cornified epidermis occurs with disappearance of the papillae, increase of the collagen in the corium and fibrosis of the fatty tissue. The muscles, most conspicuously the skeletal musculature and the muscles of deglutition and respiration, become dull, gray-yellow or pale red, firm and rubbery or soft and doughy, and hemorrhagic and friable. Later they show fibrosis, rarely with calcification. The endomysium and perimysium show edema with diffuse infiltration by round cells, including lymphocytes, large mononuclears, plasma cells, polymorphonuclear leukocytes and occasional mast cells. The muscle fibers undergo loss of striation, fragmentation of fibrils, and granular, hyaline or waxy degeneration with vacuolation or rupture. Bleb formation in the sarcolemma occurs frequently. The possibility that a virus is the etiologic agent is considered. Two cases are reported. In one the creatine content of the muscles was diminished.

FREDERICK STENN, Chicago. [ARCH. PATH.]

COOPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS: CARDIOVASCULAR SYPHILIS. I. UNCOMPLICATED SYPHILITIC AORTITIS: ITS SYMPTOMATOLOGY, DIAGNOSIS AND TREATMENT. H. N. COLE and L. J. USILTON, Arch. Int. Med. **57**:893 (May) 1936.

In an analysis of the records of 6,253 patients it was found that cardiovascular syphilis was nearly three times more frequent in Negro than in white patients. The greatest incidence occurred in the age group from 35 to 45.

In 10 per cent of the cases in which the duration of the infection was known the condition developed to a point at which it could be detected in less than five years. Adequate treatment in the early stages of the disease in this series prevented the development of this complication for the first five years.

In 72 per cent of 255 cases the Wassermann reaction of the blood was positive, and in 49 per cent of the cases in which the spinal fluid was examined it showed evidence of involvement.

In a group of 935 patients with early syphilis observed for from three to ten years the percentage of cardiovascular syphilis was 1.6. In a smaller group followed from ten to twenty years it was 6.7 per cent. If, however, treatment had been adequate and regular in the early stages of the disease none of the graver forms of cardiovascular syphilis were found in patients followed for from three to twenty years.

Adequate treatment instituted after the detection of uncomplicated syphilitic aortitis was of definite value and helped to prolong life for several years. Of the patients who received such treatment, 63 per cent were living and free from symptoms, showing no progression of the syphilitic lesion. Only 49 per cent were living after inadequate treatment.

In comparing the effect of small and large doses of arsenicals it was found that the use of small doses increased the duration of life by twenty months more than did large doses.

It is recommended that preliminary courses of soluble or insoluble heavy metal be given in the treatment of cardiovascular syphilis.

GENERALIZED DISCOLORATION OF THE SKIN RESEMBLING ARGYRIA FOLLOWING PROLONGED USE OF BISMUTH: A CASE OF "BISMUTHIA." H. C. LUETH, D. C. SUTTON, C. J. MCMULLEN and C. W. MUEHLBERGER, Arch. Int. Med. **57**:1115 (June) 1936.

In the case reported the pronounced general pigmentation of the skin was a striking feature. The most prominent areas exhibiting the richest color were the forehead, the face, the neck and the dorsa of the hands. The remainder of the

skin was of a drab, ashen hue, the lightest color being observed on the inner aspect of the thighs and on the scrotum. The buccal and pharyngeal mucous membranes showed a deep indigo-purple-black pigmentation.

This pigmentation was the result of continuous ingestion of insoluble bismuth salts for eighteen years, during which time the rate of absorption may have been altered by a chronic ulceration of the colon.

TULAREMIC PNEUMONIA, PERICARDITIS AND ULCERATIVE STOMATITIS. S. B. PESSIN, Arch. Int. Med. **57**:1125 (June) 1936.

Pessin gives a complete report of the observations at autopsy and of the results of histologic examination in a case of tularemia which occurred in a white woman of 55. The skin showed no gross lesions. The tongue presented several grayish red shallow ulcers from 0.5 to 2 cm. in diameter. The lower gum was also ulcerated.

A review is given of all reported cases in which necropsy was performed, and emphasis is laid on the importance of publishing all reports of autopsies in cases of tularemia.

LYMPHEDEMA (ELEPHANTIASIS) OF THE EXTREMITIES CAUSED BY INVASION OF LYMPHATIC VESSELS BY CANCER CELLS: REPORT OF TWO CASES. H. MONTGOMERY, Arch. Int. Med. **57**:1145 (June) 1936.

The lymphedema (elephantiasis) in one of Montgomery's cases occurred in the leg as a result of a squamous cell epithelioma extending from the ankle to the groin. The probable cause in the second case was direct extension of a pleural endothelioma to the lymphatic structures of one arm.

Cases of lymphedema of the extremities due to metastatic invasion of lymph nodes are rather frequent, but the type of disorder reported here, in which the lymphatic channels were packed with tumor cells, is uncommon.

In the case of elephantiasis of the arm and trunk malignant degeneration was not suspected as the cause until a biopsy was made. JAMIESON, Detroit.

THE RELATIONSHIP OF TUBERCULOSIS TO THE TUBERCULODERMAS. HENRY E. MICHELSON, Journal-Lancet **56**:463 (Sept.) 1936.

The author deprecates arbitrary classifications of cutaneous tuberculosis since such classifications can be applied accurately only to the stabile forms of tuberculoderma and not to the labile forms. He emphasizes the necessity for considering the internal source of infection in cases of both forms since in nearly all cases cutaneous tuberculosis is an external manifestation of such an infection, the morphologic characteristics merely giving evidence of the allergy of the host or of some inherent tendency of the person.

SCABIES: FURTHER OBSERVATIONS ON ITS TREATMENT WITH PYRETHRUM OINTMENT. S. E. SWEITZER, Journal-Lancet **56**:467 (Sept.) 1936.

Results of treatments with pyrethrum ointment in a series of 618 cases of scabies were previously reported by Sweitzer and Tedder. Sweitzer now reports a second series of 595 cases and describes the manner of treatment and the results obtained. He regards this ointment as a clean, effective and valuable remedy.

LYNCH, St. Paul.

NEONATAL DERMATITIS. H. C. CARTER and H. A. OSBORN, Brit. M. J. **1**:465 (March 7) 1936.

Under this heading, the following entities are grouped: (1) simple infantile dermatitis (Jacquet); (2) syphilitic dermatitis; (3) erysipelas neonatorum; (4) bullous dermatitis due to mechanical or chemical irritants; (5) pyodermatitis.

The latter is subdivided into (*a*) folliculitis; (*b*) subepithelial dermatitis (pemphigus neonatorum), and (*c*) deep cutaneous abscesses.

The article concerns itself principally with a discussion of subepithelial dermatitis and the experiences of the author with this condition at the Mill Road Infirmary, Liverpool, England. The term "subepithelial dermatitis" is preferred by the authors to the usual designation "pemphigus neonatorum." In 1932, in thirteen cases investigated, all the cultures contained a growth of Staphylococcus aureus. In an epidemic in 1933, two strains of Staphylococcus citreus were recovered from the blisters; one fermented milk and produced acid; the other clotted milk. These strains also fermented sugars and produced indole. They were not recovered in subsequent cases except in those occurring during one epidemic in which the mortality was low. Ninety-four cases in all were studied, and in none were partially anaerobic strains of streptococci obtained which resembled those usually observed in cases of impetigo contagiosa bullosa of older infants. It is therefore concluded that there is no bacteriologic proof that subepithelial dermatitis is an infantile form of impetigo contagiosa. Examination of sections of skin taken from affected areas on infants who died showed that the spread took place between the epidermis and the corium. The authors conclude that "the only difference between exfoliative dermatitis and subepithelial dermatitis is one of degree." They also suggest that in referring to the more severe and fatal type of the disease the term "epidermatitis exfoliativa" may be used.

The site of the original lesion helps to determine the source of infection; involvement of the napkin area incriminates napkin and nursing technic; that of the umbilical region points to lack of care on the part of the person responsible for dressing the baby.

The following technic was used in treating seventy-four patients, all of whom made rapid and uneventful recoveries: The blister was washed with ether, a fine capillary pipet was pushed into it, and the contents was evacuated for study; then another pipet containing a 20 per cent solution of silver nitrate was inserted into the same puncture and the solution was injected. The lesion was covered with antiseptic dusting powder. Usually only one injection proved necessary. Occurrence of cases ceased when laundry methods were revised and sterile clothing was supplied for the infants. The authors state that the laundry workers must be under medical supervision in order that carriers of staphylococci may be detected. In their opinion, fatal termination is ". . . due to late diagnosis and inefficient treatment."

APPEL, Boston.

CHRONIC GLANDERS. J. F. BURGESS, Canad. M. A. J. **34**:258 (March) 1936.

Burgess points out that glanders is a widespread disease caused by Bacillus mallei and chiefly affecting horses, mules and asses. In horses the disease is manifested by nasal discharge, submaxillary enlargements and abscesses in the neck. Glanders in man is usually related to infection in a horse. The disease, however, is rarely seen in man, even in the district about Istambul, Turkey, where, it is said, 90 per cent of the horses show evidence of the infection. Burgess was able to find records of approximately 200 cases of human glanders in the medical literature.

In man the disease may be acute or chronic; in the former type a fatal outcome is almost invariable; when the condition is chronic, the course is frequently long, but cure occasionally occurs. The infection may enter through an abrasion of the skin, through the mucous membranes (particularly of the nose) and, occasionally, through the conjunctiva of the eye. The disease may also begin as an acute infection simulating disease of the respiratory tract, typhoid or rheumatic fever, no demonstrable portal of entry of the organism being present. The clinical manifestations of the disease are various.

The primary lesion in the skin is a vesicopustule. Lymph nodes draining the area enlarge but rarely ulcerate. The inflammation spreads, and in the cases of acute involvement a severe systemic reaction develops. Generalized eruptions

may appear. When the disorder is chronic it proceeds to abscess formation and ulceration. Metastatic foci may develop in other parts of the body, particularly in the subcutaneous tissue and muscles, but the joints and lungs may also be affected. The disease has been known to occur in the spleen, liver and brain. Periods of latency are not unusual, lasting over a period of some years. B. mallei may often be demonstrated in the discharges from active lesions. Cultures should be made on glycerin agar and potato; pus may be inoculated intraperitoneally into male guinea-pigs. The Strauss reaction should be looked for. The mallein reaction is considered fairly specific. A reaction consists of a local erythematous swelling with edema and infiltration at the site of the injection lasting forty-eight hours and an associated systemic disturbance with fever. The complement fixation test is also a reliable method for the diagnosis of glanders. The agglutination test is used, but its value is doubtful. A precipitin reaction is not considered trustworthy.

In the case reported by Burgess, that of a butcher aged 59, the duration of the infection was fifteen years. The disease was limited to the genitocrural and axillary areas. The clinical picture suggested lymphogranuloma venereum, granuloma inguinale, tuberculosis, syphilis, mycotic process and yeast infections, but all these diseases were excluded from consideration. B. mallei was not demonstrated or cultured. The mallein test resulted in a strong cutaneous reaction. The complement fixation test for glanders was also strongly positive, the reaction being 4 plus. At the end of three months the same result was obtained on repetition of the test.

Antimallein serum was given subcutaneously for two months in doses of from 2.5 to 10 cc. every three to five days. Clinical improvement resulted and was accompanied by a reduction in the intensity of the reaction to the complement fixation test.

EXPERIMENTAL ARSPHENAMINE DERMATITIS. F. E. CORMIA, Canad. M. A. J. **34**:272 (March) 1936.

Cormia, working in Montreal, Canada, found that it was possible to sensitize guinea-pigs to neoarsphenamine. There was a marked difference in the sensitizing power of different brands of neoarsphenamine; different lots of the same brand also had different sensitizing indexes. The patch test was of no value in the detection of cutaneous hypersensitivity to neoarsphenamine in guinea-pigs. Cutaneous sensitivity to the arsenicals as shown by reaction to intradermal injections was thought to be confined to the trivalent group. It was found that two separate intradermal injections of neoarsphenamine are necessary to cause the development of cutaneous sensitivity in guinea-pigs. The intravenous injection of neoarsphenamine in guinea-pigs previously sensitized by intradermal injections of the same drug produced local reactions and may be an accurate method of determining cutaneous sensitivity to the arsphenamines.

NEUROSYPHILIS. J. C. HOSSACK and S. C. PETERSON, Canad. M. A. J. **34**:284 (March) 1936.

Hossack and Peterson plead for more consideration of the possibility of syphilis in cases of obscure disorders. To prevent involvement of the nervous system with destruction of nerve tissue, adequate treatment of patients with early syphilis must be given; the authors advise one year of continuous therapy consisting of thirty injections of neoarsphenamine and thirty injections of a bismuth salt given by the alternating or overlapping method. At the end of six months a Wassermann test is made; if this is positive an examination of the spinal fluid is also made; if the complement fixation test is negative the spinal fluid is not examined until the end of the year of treatment. Two courses of ten injections of a bismuth salt with or without neoarsphenamine are given in the second year. Neurosyphilis may be divided into three subgroups—asymptomatic, early and late. Hossack and Peterson advise malaria therapy in all forms of neuro-

syphilis; this should be followed by treatment with the arsenicals and with heavy metals. The best results are obtained when treatment is given before actual destruction of nerve tissue occurs; however, even when treatment is given in a late stage the progress of the disease may usually be stopped.

LEWIS, New York.

SENSITIVITY OF DIFFERENT SITES OF THE SKIN OF THE MOUSE TO CARCINOGENIC AGENTS. J. M. TWORT and C. C. TWORT, J. Path. & Bact. **42**:303, 1936.

The skin in the interscapular region is usually more sensitive to carcinogenic agents than that covering the sacral or abdominal regions, while the soles are apparently the most resistant. An animal which is sensitive in one area is usually relatively sensitive in another area. When areas of skin of the same animal are compared it is found that an area which is more sensitive to the production of benign tumors is usually but not necessarily more sensitive to the production of malignant tumors. There is no evidence to show that a benign tumor per se in one area influences the production of a benign or a malignant tumor elsewhere, but there is some evidence that a malignant tumor produced in one area retards the development of a malignant tumor elsewhere. This may be due to the debilitating effect of the first malignant tumor. Although the average type of tumor varies with different agents, the site of painting appears to have much less effect in determining the type of tumor. The application of carcinogenic agents in one area retards tumor formation in another, the carcinogenic potency being only about one-half to two-thirds that of the control. The debilitating effect of the agent on the animal is presumably the cause. Previous applications of oleic acid to a given site cause an increase in the carcinogenic potency of the tar when this is applied at the same site. When the tar is applied at a site different from that previously painted with oleic acid the carcinogenic potency falls below that of the control. Again, the lowering effect is presumably due to the general debilitating effect of the oleic acid.

FROM THE AUTHORS' CONCLUSIONS. [ARCH. PATH.]

THE RÔLE OF PREVIOUS TRAUMATISM AND "CELLULAR MEMORY" IN PSORIASIS. M. A. KISSMEYER, Ann. de dermat. et syph. **5**:1085 (Dec.) 1934.

A tendency for psoriatic lesions to develop at the site of traumatic injury in some patients with psoriasis is well known (phenomenon of Köbner). This author reports an extraordinary disposition of psoriatic lesions in a young girl on the back of whose hand the two letters E A appeared clearly in typical psoriatic papules. The explanation was that two years previously her brother had pricked his initials at this site on her hand with a pin, making only superficial scratches. No india ink or other colored substance was used. The slight lesions promptly healed and left no trace. The author refers to the phenomenon as "a truly remarkable memory of the cells," by which a tissue alteration, however slight, may after years be "recalled" by the epidermal cells and, "the occasion presenting itself," give rise to a psoriatic manifestation. He regards this fact as lending strength to the theory that psoriasis is a parasitic disease.

HISTOLOGIC RESEARCHES ON THE TRANSVERSE FOLDS OF THE NAILS (BEAU). JEAN ALKIEWICZ, Ann. de dermat. et syph. **6**:37 (Jan.) 1935.

From a histologic study of the nails the following conclusions were drawn: 1. The groove of Beau is not a lesion of the surface of the nail alone but affects all the layers. 2. In a longitudinal section of a nail bearing a groove one observes an oblique passage formed of altered cells. 3. The lesions of the cells express themselves by (*a*) thinning, (*b*) altered color and (*c*) weakened union. The thinness is the cause of the depression of the surface and of the development of the groove. 4. The cellular alteration is often the result of an inflammatory discharge of the matrix; sometimes there are metabolic disturbances which are

responsible for the production of diseased cells. 5. In regard to color, the author says: "I have observed some pathologic modifications surrounding intra-ungual hematomas." The article is accompanied by excellent photomicrographs.

GANDY, Houston, Texas.

INTRACUTANEOUS EPITHELIOMA OF RABBITS AND ITS IMMUNIZING EFFECT. A. BESREDKA, I. MAGAT, P. LAVAL and P. BESNARD, Ann. Inst. Pasteur **56**: 125, 1936.

Epithelioma of rabbits (Brown and Pearce, 1923) was successfully induced in from 90 to 95 per cent of animals inoculated intratesticularly. Metastases were numerous and widely spread. However, intracutaneous injections were followed in about five days by intracutaneous tumors, which increased in number for several weeks and then were gradually resorbed, with no metastases. The histologic picture of these tumors was similar to that of malignant tumors, and the virulence was not reduced. Inoculation into one flank of a rabbit was followed by a general cutaneous immunity; subsequent injection into the opposite flank resulted in no formation of a tumor. In fact, after cutaneous tumors were resorbed immunity to intratesticular injections was manifested.

MARSHALL, Berkeley, Calif. [ARCH. PATH.]

TREATMENT OF PLANTAR WARTS. PAUL MICHON, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Nancy) **42**:36 (Jan.) 1935.

Michon regards a combination of application of carbon dioxide snow and galvanocautery as the best method of treating plantar warts, and cites several cases in which he obtained successful results. Blanching of the lesion with carbon dioxide snow, aside from its own cauterizing effect, provides anesthesia for the actual cautery, and the pain is negligible. The number of seances varies from one to five, according to the age and size of the wart. The method obviates the necessity for local anesthesia, which is always objectionable in the plantar region. There is no hemorrhage or after pain, and at no time is the patient incapacitated for walking. Michon urges more widespread use of the method.

GANDY, Houston, Texas.

CONGENITAL GENERALIZED KERATODERMA WITH ANOMALY OF THE NAILS AND HAIR AND KERATITIS. ROBERT DEBRÉ and G. DESBUQUOIS, Bull. Soc. de pédiat. de Paris **32**:335 (June) 1934.

A girl 9 years old had always had a dry rough skin, especially on the lateral parts of the palms of the hands. She made normal progress mentally and physically. The history stated that at the age of 3 years she began to show grayish spots on the nails of the third and fourth fingers of both hands, which gradually became more marked; then the nails were shed, and the nail beds began to suppurate. Most of the nails of the hands and feet became involved. The scalp was very dry and thickened and was covered by sparse hairs, and the eyebrows and eyelashes were practically absent. During the past year marked bilateral keratitis had developed. It is thought that the condition which has been described as congenital keratosis palmaris et plantaris is but a milder form of the affliction that was present in this case. The etiology is probably connected with some endocrine disturbance. There was no evidence of syphilis or tuberculosis in this child. In the discussion it is suggested that treatment with iodide ionization over a period of years might yield some improvement of the keratoderma.

BENJAMIN, Montreal, Canada. [AM. J. DIS. CHILD.]

DISSEMINATED GANGRENE OF THE SKIN IN EARLY CHILDHOOD. R. TURQUETY, J. de méd. de Paris **56**:9 (Jan. 9) 1936.

Primary gangrene of the skin occurring in debilitated infants is described. The anatomicopathologic and bacteriologic changes and the theories of pathogenesis are discussed. In the cases reported by the author no organisms were observed in the lesions, although the pneumococcus was isolated from the blood. The author, however, thinks that the pneumococcus was not the cause of the gangrene but that it was present in association with terminal pneumonia.

LESLIE, Evanston, Ill. [AM. J. DIS. CHILD.]

STUDY OF SUBSTANCES WHICH WHEN ADDED TO CULTURE MEDIUMS DO NOT HINDER THE GROWTH OF FUNDI BUT DO LIMIT THAT OF BACTERIA. G. SAUTHOF, Dermat. Wchnschr. **101**:1245 (Oct. 5) 1935.

The author attempted to limit the growth of staphylococci without affecting that of Trichophyton gypseum. He used both the Sabouraud medium and that designated as Grutz III. Arsenic was first tried but was of no help. Chiniofon powder added to Sabouraud's medium in strength of from 1 to 2 per cent prevented the growth of staphylococci without affecting that of the trichophyton. The Grutz III medium produced the same effect in from 1.25 to 1.75 per cent concentration.

MUCUS PAPULES (CONDITION WITH HISTOLOGIC RESEMBLANCE OF LICHEN MYXOEDEMATOSUS). H. NEUMANN, Dermat. Wchnschr. **101**:1263 (Oct. 12); 1294 (Oct. 19) 1935.

In a 39 year old woman a group of nodules developed on the inner surface of the right arm at the elbow. Later scattered nodules developed on the other extremities, but the largest number remained on the right arm. The lesions started as papules measuring 7 or 8 mm. in diameter. Some increased in size, reaching that of a split pea, and a central dimple developed which presented a light brown pigmentation. Histologic examination showed essentially a mucus production in localized areas situated chiefly in the deep portion of the cutis. There was a moderate infiltration of round cells, leukocytes and a few plasma cells. Clinically there were no inflammatory symptoms and no subjective sensations. The literature was carefully reviewed, and the only report of a similar condition was one by Kreibich in 1920.

URTICARIA FROM THE INGESTION OF POPPY SEEDS (PASSIVE TRANSFER OF THE SENSITIVENESS). PAUL FASAL, Dermat. Wchnschr. **101**:1268 (Oct. 12) 1935.

In a 28 year old woman who had had eczema for several years there developed sensitiveness to poppy seeds, shown by an urticaria occurring a short time after the seeds were eaten. Passive transfer of the sensitiveness to a nonsensitive person by the Prausnitz-Küstner method was effected.

THE FACIAL EXPRESSION AS A NEW DIAGNOSTIC SIGN OF MOLLUSCUM FIBROSUM (RECKLINGHAUSEN'S DISEASE). RILLE, Dermat. Wchnschr. **101**:1432 (Nov. 16) 1935.

The author believes that in many instances the presence of molluscum fibrosum may be detected by the typical facial expression. The manifestation consists of a tired sleepy apathetic bored or resigned appearance. Rather often too the skin of the face is browner than normal.

SUPERFICIAL EPITHELIOMATOSIS. J. DÖRFFEL, Dermat. Wchnschr. **101**:1437 (Nov. 16) 1935.

In a group of 200 patients with epithelial malignant disease the author observed 18 cases of superficial epitheliomatosis. Of these 14 were in women. The clinical and microscopic features of this type of neoplasm are reviewed.

TAUSSIG, San Francisco.

SO-CALLED PAGET'S DISEASE AND DEVELOPMENT OF INTRA-EPIDERMAL CARCINOMA. KARL ZIELER, Dermat. Wchnschr. **101**:1441 (Nov. 16) 1935.

Paget's disease is a clinical and anatomic expression of the intra-epidermal extension of carcinoma. The growth in the epidermis may mask the underlying carcinoma. The disease rarely starts in the nipple or gland but usually begins in the lactic duct, spreading intra-epidermally to the skin as well as to the glands.

TAUSSIG, San Francisco.

RADIAL SCARS AROUND THE MOUTH WITHOUT CONGENITAL SYPHILIS. FRIEDRICH DIETEL, Dermat. Wchnschr. **101**:1450 (Nov. 16) 1935.

A 40 year old man presented scars radiating from the mouth. There was no evidence or history of congenital or acquired syphilis. He had had a severe eczema, which apparently caused the scars.

CHRONIC ALEUKEMIC MYELOSIS WITH THE CUTANEOUS MANIFESTATIONS OF DERMATITIS HERPETIFORMIS OF DUHRING. H. OPFER, Dermat. Wchnschr. **101**:1479 (Nov. 23) 1935.

A 63 year old man had an eruption which started on face and neck and gradually spread over most of the body. The individual lesions started as small bullae on a slightly infiltrated base. The bullae broke, and crusts formed, healing to leave a pigmented and indurated lesion. Pruritus was intense. The clinical appearance suggested a possible dermatitis herpetiformis and the first test with sodium iodide was positive, but subsequent tests were negative. The blood count was within normal limits. Excision of one of the cutaneous lesions showed the typical microscopic picture of aleukemic myelosis. TAUSSIG, San Francisco.

DARIER-ROUSSY'S SARCOID: AN ATYPICAL CASE. ALBIN PROPPE, Dermat. Ztschr. **72**:311 (Jan.) 1936.

Proppe reports the case of a patient who had had a subcutaneous tumor of the cheek which was removed surgically three times. The third time histologic examination confirmed the diagnosis of Darier-Roussy's sarcoid. Three years later typical lupus vulgaris developed in the scar. TAUSSIG, San Francisco.

LOCAL "RESECONDARIZATION," I. E., REAPPEARANCE OF EFFLORESCENCES OF SECONDARY SYPHILIS AFTER ROENTGEN RADIATION. R. LEWITH, Dermat. Ztschr. **72**:326 (Jan.) 1936.

A 30 year old woman had an ulcerative lesion of the tonsil. The Wassermann reaction of her blood was negative, and the histologic picture of material from the lesion suggested tuberculosis rather than syphilis. She was given roentgen radiation, after which an eruption typical of secondary syphilis developed. The Wassermann reaction became positive, and all the manifestations cleared when antisyphilitic therapy was started. The author dismisses the possibility of the

tonsillar condition having been a primary lesion on account of the clinical picture. He concludes that a tertiary syphilis was activated by the action of the roentgen rays, as it has occasionally been reported to be by trauma.

TAUSSIG, San Francisco.

A SIMPLE TREATMENT OF FURUNCULOSIS WITH ARNING'S TINCTURE AND SULFONATED BITUMEN. ERICH HOFFMANN, Dermat. Ztschr. **72**:332 (Jan.) 1936.

Arning first reported the use of his tincture in 1901. It consists of 1 part of anthrarobin, 4 parts of tumenol, 10 parts of ether and sufficient tincture of benzoin to make 30 parts. Hoffmann has found that painting incipient furuncles and sites of folliculitis with this preparation is often curative. When the patients are seen later this treatment may be combined with the application of sulfonated bitumen suggested by Unna.

TAUSSIG, San Francisco.

THE DIFFERENT SECRETIONS AND BODY FLUIDS IN RELATION TO THEIR ANTIGENICITY IN THE STORM REACTION. R. TIHARA, Hihu-to-Hitunyo **4**:174 (April) 1936.

The allergen which is employed in the Storm reaction is a fluid extract of dander from a person with a healthy skin, chiefly from the extremities. Tihara studied danders from skins variously affected with such diseases as psoriasis, seborrhea, eczema and exfoliative dermatitis, as well as various substances of animal and plant origin. He attempted to learn whether various other products of the human body and its functions (blood serum, urine, feces, saliva, spinal fluid, blister fluid) might give a Storm reaction in susceptible persons. The fluids were run through the Chamberland filter, and phenol (0.5 per cent) was added. The feces were diluted to 10 per cent with saline solution and filtered and phenol (0.5 per cent) was added. Each test was controlled by a simultaneous test with the regular Storm allergen, and the results are given in tables in parallel columns.

The resemblances in the results are not sufficiently extensive or constant to justify considering any of the experimental substances as a substitute for the Storm allergen. Their modes of action seem to be different from that of the Storm allergen since they are noticeably weakened by dilution and heating at 60 C. for thirty minutes and on heating become cloudy, leading Tihara to the belief that at least part of the reagens in these substances are "albumin-like."

THE INFLUENCE OF ECZEMATOUS CHANGES IN THE SKIN ON RENAL FUNCTION: IV. ECZEMATOUS CHANGES IN THE SKIN AND ALIMENTARY ALBUMINURIA; V. ECZEMATOUS CHANGES IN THE SKIN AND ALIMENTARY GLYCOSURIA. I. MIYAKE and I. OYAMA, Jap. J. Dermat. & Urol. **39**:119; 127 (Feb.) 1936.

In order to differentiate the ingested raw egg white which passes over into the urine of rabbits from the animals' own serum albumin, roosters were rendered sensitive to the serum albumin of rabbits and the percentage in the total albumin of raw egg white was estimated by means of Esbach's albuminometer, which recorded differences in intensity of precipitation between the serums sensitized to the two substances and the urine of the rabbit to be tested. Artificial (croton oil) dermatitis evidently affected the metabolism of albumin (albuminuria), but the results differed from those obtained in cases of artificial (uranium salts) nephritis. The dermatitis did not appear to induce any changes exceeding the physiologic limits of variation when 0.5 Gm. of dextrose per kilogram of body weight was injected intravenously.

The results of the studies on this subject indicate that a decrease of renal function is brought about by the artificial dermatitis. However, too many extraneous factors are at work in these experiments to permit one to conclude that the results are due to the effect on the renal function alone.

Society Transactions

AMERICAN DERMATOLOGICAL ASSOCIATION, INC.

C. Guy Lane, M.D., *President*

Boston, June 3, 1936

Fred D. Weidman, M.D., *Secretary*

Necrobiosis Lipoidica Diabeticorum. Presented by Dr. Arthur M. Greenwood, Boston, and Dr. Ethel M. Rockwood, Boston.

Case 1.—M. R., a female, has had the disease for five years; the approximate duration of the diabetes, which is poorly controlled, is five years.

The total cholesterol content of the blood was from 156 to 179 mg. (normal content, 230 mg.); the sugar content varied from 240 to 360 mg., and the nonprotein nitrogen content was 33 mg., per hundred cubic centimeters.

Case 2.—Mrs. M. C. has had the disease for eight years; the approximate duration of the diabetes is nine years.

The sugar content of the blood varied from 180 to 620 mg. per hundred cubic centimeters.

This patient states that she sustained an injury, and she has received some roentgen therapy.

Case 3.—Mrs. M. V. has had the disease for nine years; the approximate duration of the diabetes, which is poorly controlled, is fourteen years.

The total cholesterol content of the blood was 265 mg.; the sugar content varied from 160 to 560 mg., and the nonprotein nitrogen content was 40 mg., per hundred cubic centimeters.

Case 4.—Miss S. K. has had the disease for six years; the duration of the diabetes is eight years.

The total lipid content of the blood was from 810 to 620 mg. (normal content, 700 mg.); the total cholesterol content, from 293 to 228 mg.; the cholesterol ester content, 195 mg. (normal content, from 150 to 160 mg.); the phospholipin phosphorus content, from 11.6 to 10.7 mg. (normal content, from 9 to 10 mg.), and the sugar content, from 270 to 350 mg., per hundred cubic centimeters.

A section is presented.

Case 5.—H. M., a female, has had the disease for seven years; the approximate duration of the diabetes is seven years.

The total cholesterol content of the blood was from 228 to 286 mg., and the sugar content, from 180 to 350 mg., per hundred cubic centimeters.

This patient exhibits an atypical necrobiosis, with oyster shell crusts consisting of irregular verrucous elevations. A grayish material expressed from the lesions showed no growth on culture.

A section is presented.

Case 6.—Mrs. H. A. has had the disease for seven years; the approximate duration of the diabetes is seven years.

The total cholesterol content of the blood was 252 mg.; the sugar content, 430 mg., and the nonprotein nitrogen content, 37 mg., per hundred cubic centimeters.

The diabetes was badly controlled from 1930 to 1935. The sugar content of the blood was always above 200 mg. per hundred cubic centimeters. The patient has received roentgen therapy.

The results of biopsy were consistent with the diagnosis of necrobiosis.

Case 7.—Mrs. C. M. has had the disease for eighteen years; she is not diabetic.

The total lipid content of the blood was 723 mg.; the fatty acid content, 421 mg.; the total cholesterol content, 269 mg.; the free cholesterol content, 74 mg.; the cholesterol ester content, 195 mg.; the phospholipin phosphorus content, 9.8

mg.; the sugar content, 100 mg., and the nonprotein nitrogen content, 29 mg., per hundred cubic centimeters. The ratio of free to total cholesterol was 28:100, and that of ester to total cholesterol was 72:100.

This patient states that she sustained traumas eighteen, ten and five years ago. The injured area was always sensitive, and it broke down four years ago.

CASE 8.— Mrs. R. S. has had the disease for five years; the diabetes has been present for approximately five years.

The total lipid content was from 1,244 to 816 mg.; the total cholesterol content, from 312 to 287 mg.; the cholesterol ester content, from 242 to 220 mg.; the phospholipin phosphorus content, from 16 to 12.3 mg.; the sugar content, from 170 to 190 mg., and the nonprotein nitrogen content, from 29 to 34 mg., per hundred cubic centimeters.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: When I consider the cases presented the questions that come to my mind are: Do the manifestations represent an entity? Is the condition diabetic or potentially diabetic, and does a diagnosis of necrobiosis indicate that the patient is or will become diabetic? At present the association of the condition with diabetes is taken for granted, but further observation may show that necrobiosis can occur in association with other conditions. I think that one should bring out that the color of the lesions of necrobiosis need not be cerise, for some lesions that were almost purple have been observed. The history of trauma seems to be important, but the members will note that one of the patients presented had a rather extensive scar on the elbow resulting from an injury and that no necrobiotic plaque developed at that site, even though fully developed plaques of necrobiosis were present on the legs. Therefore, trauma certainly will not always produce such lesions in a certain person. I still feel that the condition is related to the general process of diabetic gangrene. In fact, the name itself, if accepted, signifies that. As knowledge of this condition enlarges, one observes microscopic sections showing changes that look surprisingly like xanthoma, and in some sections sent to me by Professor Kren many giant cells but none of the Touton type were present. A simple explanation would be to say that there is a series of conditions from xanthoma to gangrene, necrobiosis occupying about the middle point. I do not feel that the presence of necrobiosis is in any way valuable in determining the severity of the diabetes, for necrobiosis has been known to occur in cases of both mild and severe diabetes, and the progress of the diabetes seems to have no influence on the lesions. The treatment used by my co-workers and me has not brought about much change, although improvement has been reported by others with the local use of insulin and roentgen therapy. All in all, necrobiosis is a condition worthy of consideration and study.

DR. ALEXANDER MARBLE, Boston: My associates and I, working with Dr. Elliott P. Joslin, have been greatly interested in the cases of necrobiosis lipoidica diabetica which have occurred among our diabetic patients. We have been fortunate in having the cooperation of Dr. Greenwood. In every instance he has either made the diagnosis originally or confirmed it and has directed treatment of the cutaneous lesion.

In our own practice the condition has been recognized in nine diabetic persons, eight of whom are still living. All of the patients except two have been females 25 years of age or younger. The other two patients were 32 and 52 years of age, respectively.

We have been particularly interested in studying the lipid content of the blood of these patients, including the total cholesterol content, the free and combined cholesterol content, the phosphatide content and the total lipid content. The studies are as yet incomplete, but some statement is warranted at the present time. Of the eight living patients six are known to have had at one time or another during the course of the study a total cholesterol content above 230 mg. per hundred cubic centimeters of blood, the upper limit arbitrarily chosen as normal. However, the elevation has in every instance been slight or moderate, no value

being above 312 mg. per hundred cubic centimeters. The ratio of cholesterol esters to total cholesterol has been uniformly within normal limits. In two patients total lipid values of over 800 mg. per hundred cubic centimeters have been encountered, and in these the phosphatide content of the blood was correspondingly elevated. A summary of our results to date shows that usually there is a moderate increase of all lipoid elements of the blood in patients with this condition. The significance of this is not entirely clear, since this degree of increase in blood lipids is frequently seen in diabetic patients who do not have cutaneous complications. It is interesting and highly important to note, however, that one of the patients shown here today is not diabetic, as proved by the results of a dextrose tolerance test, and yet she has cutaneous lesions indistinguishable from those exhibited by the diabetic patients. Furthermore, the cholesterol content of her blood is also moderately elevated, the result of one determination being 252 and that of another 269 mg. per hundred cubic centimeters. This adds significance to the increase in blood lipids present in the diabetic patients.

We are hoping to obtain representative biopsy material from one or more of our patients so that it may be studied not only by histochemical methods but also by regular chemical procedures in order to determine any abnormality in the lipoid content of the excised tissue.

Dr. Michelson suggested that the process in necrobiosis lipoidica diabetica is more closely allied to diabetic gangrene than to diabetic xanthoma. In this connection, however, it is worth while to note again (1) that one of the patients is not diabetic and (2) that the greater number of our patients with this condition are young persons in an age group in which, even in association with diabetes, well marked vascular involvement would be rare.

Dr. J. Gardner Hopkins, New York: I was greatly interested in seeing this remarkable group of patients. It is illuminating as to the apparent frequency of this dermatosis in association with diabetes. That diabetes is not an essential cause is evidenced by the occasional occurrence of apparently identical lesions in nondiabetic persons. A convincing picture of the lesion and the histologic changes was presented. My associate, Dr. Gross, has been studying an interesting example of this. One thing has rather intrigued me. I wonder whether Dr. Greenwood has found any evidence of a possible connection between this condition and the activity of the thyroid. In one case in which unusually nodular lesions were present there was a history that the thyroid had been removed. The patient had diabetes. The nondiabetic patient I referred to stated that she had taken thyroid under a physician's direction for a number of years, although when we saw her the basal metabolic rate was normal. In the diabetic patient the cholesterol content of the blood was 316 mg. per hundred cubic centimeters, and in the nondiabetic patient it was 107 mg., which was practically normal. This makes one suspect that the high cholesterol content frequently found in patients with necrobiosis is in no way responsible for the cutaneous lesions but is merely an evidence of the fact that they have diabetes.

Dr. E. P. Zeisler, Chicago: This group of cases bears out the well known dermatologic axiom that when attention is called to a new condition, cases of that condition are soon discovered. Since the first case of this disorder in the United States was shown before this association by Dr. Caro and me two years ago Dr. Michelson has reported several additional cases, and there is no longer any doubt that the condition is a new entity which was not previously recognized. All the investigation that has been done since the original work of Urbach and Balbi has not thrown any new light on the pathogenesis of the disorder. In several of the cases shown today the manifestations were typical, consisting of the buff coloring with the rose or violaceous border and the characteristic sclerodermatous consistency. In two cases, I think, the diagnosis is questionable, namely, in that of the patient with the reddish circumscribed patch around the ankle and in that of the patient who has two large lesions of the abdominal wall and no lesions around the lower extremities. That condition may be morphea.

Dr. Arthur M. Greenwood, Boston: It is interesting that all the recorded cases, with one exception, have been in females. I think there is only one case of necrobiosis lipoidica diabeticorum in a male on record.

ICHTHYOSIS HYSTRIX. Presented by DR. C. GUY LANE, Boston.

B. B., a woman aged 22, presents a generalized eruption which has been present since birth; it is most marked in the axillae, on the perineum and on the neck and is associated with general dryness of the skin. The patient complains especially of the odor, irritation and cosmetic aspect of the axillary regions.

There is a generalized ichthyosis with warty excrescences in the axillae, groins, neck and antecubital spaces.

The urine and blood were normal; the Hinton test was negative.

The patient had been given roentgen therapy to the axillae; this has brought about improvement in the hyperhidrosis. An ointment brought about improvement in the hyperkeratosis of the neck. A plastic operation on one axilla will be performed.

Biopsy of material from the axilla and of the skin over the abdomen showed papillomas and hyperkeratosis.

DISCUSSION

DR. FRED WISE, New York: I suggest the possibility of the juvenile type of acanthosis nigricans. I understand that the lesions have been present since birth, which nullifies that diagnosis to some extent, but the patient exhibits rough and papillomatous lesions that resemble the benign form of acanthosis nigricans more than anything I can think of. I do not say that ichthyosis hystrix is not present, but the eruption as a whole does not correspond morphologically to any form of true ichthyosis, and the section does not correspond to ichthyosis histologically.

DR. CHARLES J. WHITE, Boston: Does Dr. Wise think the ichthyotic lesions of this patient follow the usual distribution of acanthosis nigricans? One expects to find lesions of acanthosis nigricans especially between the buttocks and in the axillae, and in this case I did not note such lesions.

DR. FRED WISE, New York: I think the most pronounced lesions are in the axillae, where they may be ½ inch (1.27 cm.) long, and in the perianal and genital regions.

DR. C. GUY LANE, Boston: When this patient first came into the clinic my co-workers and I were very busy, and at first glance I was inclined to make a diagnosis of acanthosis nigricans, but as I examined her later I thought the eruption lacked the usual features of acanthosis nigricans, and so I changed my diagnosis to ichthyosis hystrix.

DR. J. GARDNER HOPKINS, New York: I was much interested in what Dr. Wise said. My associate, Dr. Curth, has been studying acanthosis nigricans and has called my attention to the fact that it too probably falls in the broad group of nevi in the sense that it is a localized abnormality in the skin due to some hereditary influence. The discussion indicates that the members agree on the essential point that this patient has an anomaly of the skin on a hereditary basis. Anomalies differing in appearance have been described under such a variety of names that it is difficult to agree on just which name fits in this case; but that is of small importance.

A CASE FOR DIAGNOSIS. Presented by DR. J. H. SWARTZ, Boston.

Mrs. S. T., a housewife aged 70, was admitted to the medical service of the Beth Israel Hospital on May 22, 1936. According to the family history, her father had nephritis, her mother apoplexy and a sister carcinoma of the bladder. This patient cared for her husband about fifty years ago while he had pulmonary tuberculosis. Her past history is as follows: She had erysipelas of the face on three occasions, the last attack occurring three years ago. During the past thirty years she has had many attacks of pain in the right upper abdominal quadrant; the pain radiates to the back and right scapular region, and jaundice has been present

on many occasions. No attacks have occurred since the development of her present illness. In recent months the patient has complained of frequent attacks of vertigo and faintness. Her present illness dates back one year. It began with a rash originally involving the anterior surfaces of both legs and later extending to the back and to the left hand. The lesions were pruritic, and they burned and throbbed intensely. At first they were urticarial; later they showed reddish centers, from which serum occasionally exuded. The patient states that her color has always been dark but that it has become darker during the past year. There is no history of severe nausea or vomiting or of cough, hemoptysis, night sweats or fever, and no syphilitic infection is present. The patient does not feel weak, and except for the cutaneous eruption she has been in good health.

The tongue and pharynx are clear and show no pigmentation. There are no tremors, clubbing of the fingers or cyanosis, but the fingers show hypertrophic changes. The reflexes are equal, active and normal. The entire skin is of a light chocolate color, being darker about the eyes, on the neck and under the breasts. Over the anterior surface of the lower portion of the legs and extending below the left calf are a number of irregular, circular or oval lesions which in some areas are confluent and in others are raised and show superficial ulcerations. Similar smaller and healed lesions are present over the left buttock and on the extensor surfaces of the arm. A number of white atrophic linear and circular scars are present over the body, giving the generalized dark pigmentation a mottled appearance.

The urine was normal except for a few leukocytes. The serologic reaction of the blood was negative. There was moderate secondary anemia, the hemoglobin content of the blood being 75 per cent. The differential cell count showed 73 per cent polymorphonuclear neutrophils, 22 per cent lymphocytes and 4 per cent large mononuclears. Chemical examination of the blood gave the following results: chlorides, 464 mg.; cholesterol, 277 mg.; cholesterol esters, 97 mg., per hundred cubic centimeters. The icterus index was 6.25.

DISCUSSION

DR. FRED WISE, New York: I have no definite diagnosis to offer. At first sight the lesions impressed me as possibly representing amyloid degeneration; they are not identical with the lichen planus type of degeneration but rather correspond with the other types described by Freudenthal. The histologic diagnosis in this type depends almost entirely on the fixation of the tissue and on the stain. The tissue will have to be stained for amyloid and for lipoid in order to permit a correct diagnosis. The clinical appearance is somewhat similar to that of the lesions in cases of extracellular cholesterosis, and in that condition the staining is of paramount importance for purposes of diagnosis.

DR. J. H. SWARTZ, Boston: At the time these lesions began to develop the patient noticed pigmentation which was progressive, beginning on the face and extending downward. At first my co-workers and I considered the diagnosis of hemochromatosis, but we ruled that out. I wonder what the relation is between the lesions on the legs and the pigmentation. The patient states that she has taken arsenic.

DR. H. E. MICHELSON, Minneapolis: My co-workers and I had a patient with extracellular cholesterosis whose lesions did not in any way resemble those exhibited by this patient. The disease described by Urbach and Wiethe is a familial disease, involves the face and is quite different from this patient's condition. I believe that these lesions are some form of verrucous lichen; however, stain should be made for amyloid. I doubt that any will be found because of the short duration of the condition. There is also an important neurotic element present, and the excoriation may be on that basis.

DARIER'S DISEASE (KERATOSIS FOLLICULARIS [WHITE]). Presented by DR. CHARLES J. WHITE, Boston.

P. W. G., a man aged 21, states that sixteen years ago he noticed a red blotch "something like dandruff" about the size of a dime on the posterior aspect of his

scalp. This gradually increased in size during the next six years, completely covering the scalp. Since then he has had recurrent severe attacks involving the entire scalp; at times oozing has been present. The attacks last from three days to a month, and the condition then subsides, leaving only a scaly texture. Five years ago after he sustained a sunburn the patient noted small brownish pimples on the body. These lesions have gradually increased in size, and they have never disappeared.

The skin of the forehead, scalp, neck and areas behind the ears is covered with an erythematous, oozing, crusty eruption. The entire body is covered with an eruption which fades out on the extremities into discrete papules gradually diminishing in size. Over the chest, the midsternal region and the face the lesions are confluent, scaly and somewhat moist. The lesions are follicular and vary in size from that of a pinhead to almost that of a split pea.

The urine was normal. Examination of the blood showed 4,410,000 erythrocytes, 13,400 leukocytes and 80 per cent hemoglobin. The results of the differential count were as follows: polymorphonuclear neutrophils, 59 per cent; large lymphocytes, 2 per cent; small lymphocytes, 28 per cent; monocytes, 8 per cent; eosinophils, 2 per cent, and basophils, 1 per cent. The erythrocytes and the platelets were normal. The Hinton and the Wassermann reaction were negative. The nonprotein nitrogen content of the blood was 28 mg. per hundred cubic centimeters; the serum protein content, 7.1 Gm.; the phosphorus content, 4.20 mg.; the cholesterol content, 166 mg., and the chloride content, 903 cc. of tenth-normal hydrochloric acid per hundred cubic centimeters.

DISCUSSION

Dr. Charles J. White, Boston: I thought that as the meeting is being held in Boston it might be interesting to bring to this assembly two reprints of articles by Dr. J. C. White concerning his first and second cases of keratosis follicularis. In the first case he described ten features which he noted clinically. He turned over the material for microscopic examination to Dr. Bowen, and I think the members can all see from this plate that the essential lesion is the great widening and, to a lesser extent, the deepening of the hair follicles and the subsequent production of cutaneous hair.

The second patient proved unexpectedly to be the daughter of the first, these two persons meeting after a lapse of many years in the waiting room of the clinic.

Again Dr. Bowen made the microscopic examination and discussed at length the nature of the bodies on which Darier based the name "psorospermose," by which he designated the disease. Dr. Bowen and other American scientists whom Dr. White consulted did not believe that these bodies were parasites.

Raynaud's Disease; Calcinosis Circumscripta. Presented by Dr. J. H. Swartz, Boston.

B. F., a woman aged 39, was admitted to the medical service of the Beth Israel Hospital on May 16, 1935, when a diagnosis of calcinosis circumscripta, acrodynia and Raynaud's disease was made. She reentered the medical service on Feb. 10, 1936, because of painful swelling and cyanosis of the fingers of both hands and infection of the index and fifth fingers of the left hand, of three months' duration, associated with the onset of cold weather. The condition of her fingers had become progressively worse before her admission to the hospital. She also complained of dyspnea, palpitation on exertion and occasional pains in the chest.

Examination revealed definite cyanosis of the skin, lips and finger-tips. The skin over the face was somewhat dry and plethoric, and there were a few small discrete patches of irregular reddish mottled areas. The thorax was slightly emphysematous and showed some increase in the anteroposterior diameter. The lungs were hyperresonant throughout. Both hands revealed shortening of the nails and slight shortening of the distal phalanges with broadening of the finger-tips. The skin over the fingers was firm, fixed and not movable over the underlying tissue. The left middle finger was swollen, and there was an area of blotchy

material measuring from 4 to 5 mm. in diameter in the right thumb at the junction of the second and the third phalanx; a few larger areas similarly involved were present on the anterior aspect of the right index finger. The peripheral vessels showed moderate sclerosis.

The number of leukocytes was 14,800; the vital capacity, 1,800 cc., and the basal metabolic rate, —9 per cent.

Some of the white material under the skin of the fingers removed on May 21, 1935, for histologic examination was found to be calcium.

Roentgenograms of the skull, chest, feet and long bones showed no abnormalities. Those of the kidney, bladder and ureter showed a calcified body on the left, possibly in the adrenal gland; those of the hands showed deposition of calcium under the skin. There was no evidence of gout. The changes in the soft tissue of the hands were consistent with the diagnosis of calcinosis circumscripta.

The patient remained on the medical service for twenty-six days; then she was transferred to the surgical service, where a dorsal sympathectomy on the left side was performed. The wound healed well. Examination revealed that the right arm was cold, clammy and covered with perspiration, while the left arm was warm and dry. Determinations of the temperature of the skin revealed that the left arm was from 0.5 to 3 F. warmer than the right.

MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA (KAPOSI). Presented by DR. J. H SWARTZ, Boston.

This man, aged 66, who was formerly a fruit dealer, states that the original lesion, a mole on his nose, had been present as long as he could remember. Subsequent lesions occurred after the original lesion was removed in the summer of 1931. The entire body except the anterior aspect of the chest and the abdomen is involved.

The patient states that in the summer of 1931 the original lesion was fulgurated and cleared, but it recurred in two weeks as an ulcerative lesion. Shortly afterward bluish red nodules appeared near the fulgurated area. A physician fulgurated one of the new nodules and also the original area. Since then the bluish nodules have appeared in rapid succession.

Lesions are present on all the extremities as maroon and purple nonelevated blotches. Mahogany-red to brownish black lesions are situated irregularly all over the body, on the floor and roof of the mouth and on the nose, face, eyelids, extremities and trunk. The distal portions of the extremities are discolored by a subcutaneous or intracutaneous blood red hue. In those locations the lesions are not elevated; elsewhere they assume different shapes, varying from blocks to sessile and papillomatous growths.

The Hinton reaction was negative. The results of examinations of the blood are given in the table.

Roentgen examination of the chest (Jan. 19, 1934) showed that the diaphragm was low and flat and moved well with respiration. The pulmonary fields were relatively large. The intercostal spaces were wide. The pulmonary markings were slightly more prominent than usual. The apex of the right lung was slightly less radiant than that of the left, probably owing to an old thickening of the pleura. The cardiac shadow was prominent in the region of the left ventricle and in the left upper border. The aorta was tortuous. The measurements of the heart were within normal limits. The examination showed essentially normal conditions except for evidence of arteriosclerosis and mild emphysema. The upper portion of the gastro-intestinal tract was examined on Feb. 26, 1936. The esophagus and stomach were normal. The stomach was emptying freely. There was a large diverticulum arising from the transverse portion of the duodenum.

Reports on histologic examinations were as follows: On May 22, 1931, a nodule from the nose measuring 4 mm. in diameter and partially covered by skin was seen to consist mainly of nevus tissue; there were numerous groups of nevoid cells in the corium and abundant amounts of melanin. The nevoid cells were

mature. There were no mitotic figures. The squamous epithelium was normal. Adjacent to the nevus, in the corium, was an oval region of spindle cells with elongated nuclei and scanty cytoplasm. The cells were arranged in the form of intertwining fascicles. Occasional mitotic figures were noted. Numerous capillaries were present. Another smaller focus was noted between the epidermis and groups of nevoid cells. The subcutaneous fat was also invaded by spindle cells. A third focus was noted just below the epidermis, near the nevus, in which dilated capillaries were seen surrounded by lymphocytes.

The diagnosis, as based on examination of that specimen was: nevus with small adjoining focus compatible with multiple hemorrhagic sarcoma (Kaposi's disease). On Sept. 11, 1934, a lesion from the tip of the nose and one from the left cheek were examined. Grossly they were seen as two firm purplish gray oval masses covered with skin and measuring 0.3 by 0.5 by 0.5 cm. Their cut surfaces were smooth, glistening and dark red. The diagnosis was spindle cell sarcoma. On May 29, 1935, a lesion from the hand and one from the left eyelid were examined. The two small reddish brown nodules measured 1 cm. in diameter and 1 by 1.5 cm., respectively. One was covered with a piece of dark gray rough nonulcerated skin. One section from the lesion on the hand was dark red and smooth; the other was dark pink. Both were moderately firm. The diagnosis was multiple fibrosarcoma. The presence of numerous blood vessels, which were in close relation-

Results of Examination of the Blood

Date	Hemoglobin Content, %	Erythrocytes	Leukocytes	Polymorphonuclear Neutrophils, %	Lymphocytes, %	Large Mononuclears, %	Eosinophils, %	Unclassed Forms, %
5/13/32	65	4,800,000	10,400	68	20	4	3	9
7/ 8/32	85	4,600,000	6,000	60	24	8	3	5
8/19/32*	..	4,980,000	6,100	70	22	4	0	
2/17/33†	70	.....	.....	35	45	10	4	6
1/17/34	68	3,590,000	.....	68	Large 1 Small 23	Mononuclears 8		

* The erythrocytes and platelets were normal.
† The erythrocytes showed the picture of secondary anemia.

ship to the spindle-shaped tumor cells, suggested that these growths belonged to the Kaposi type of sarcoma. On Dec. 10, 1935, two specimens from the tongue were examined. One consisted of a small resected portion of tissue measuring 1.5 by 1.5 cm. The mucosal surface was bluish white and contained on one margin a sessile polypoid mass measuring 1 cm. in diameter across its base. The greater portion of its mucosal surface was ulcerated. On section the lingual musculature was not remarkable as seen grossly. The stroma of the polyp was a homogeneous yellowish gray, moist, glistening, soft, finely granular tissue. The other specimen showed a bluish gray nonulcerated mucosal surface measuring 2.5 by 1 cm., attached to which was a soft mass of connective tissue measuring 1 by 2 by 0.8 cm.; embedded in this mass there was a small area grossly corresponding to the stroma of the polyp described. A third specimen removed from the upper lip consisted of a portion of epithelium measuring 0.5 by 0.9 cm.; the margin contained several hairs. The major portion of the surface was discolored, being dark pinkish black. No ulceration was noted. This mass cut with markedly increased resistance, and its stroma was homogeneous, hemorrhagic and finely granular. A specimen removed from the soft palate consisted of a rounded polypoid mass measuring 1.2 cm. in diameter. The mucosal surface was nonulcerated and milk white. The stroma of the polyp was soft and finely granular, pale pink and similar to the stroma described for the specimens from the tongue. The diagnosis was sarcoma. The lobulated structure of the tumor suggested a neurogenic origin, although the lesion might have been an angiosarcoma (Kaposi), as

it was richly supplied with blood vessels and contained numerous hemorrhagic areas. The previous history of a tumor showing the characteristics of Kaposi's disease was also suggestive.

Roentgen therapy was followed by flattening and paling of the lesions treated, but new lesions continued to appear. On Sept. 11, 1934, the lesion on the tip of the nose and one on the left cheek were excised for the sake of appearance. On May 29, 1935, a lesion on the left hand and one on the left eyelid were excised for the same reason. On Dec. 10, 1935, two lesions in the mouth, one on the upper lip and one on the soft palate were excised because they interfered with swallowing. By Feb. 26, 1935, 1,200 roentgens of radiation had been administered to the upper lip and 1,200 roentgens to the lesion on the left side of the face. On April 3, 1936, the patient received an additional 600 roentgens of radiation to the face. On May 8, 1936, he received an application of radium needles to the chin and upper lip for a total of 30 mg. hours each.

MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA (KAPOSI). Presented by DR. C. GUY LANE, Boston.

W. F., an Irishman aged 81, a machinist, seven years ago had a mass on the right eye which was described as consisting of two distinct, well defined indurated lesions 3.3 mm. in diameter on the border of the lower lid. The growth was dark purple. There was a small lesion on the upper lid opposite that on the lower, along the border of the cartilage. This was less defined and measured about 2.5 cm. The provisional diagnosis at that time was melanosarcoma. No pathologic report can be found. The fundi showed sclerosis, but no angiomatous changes were seen. The posterior surface of the right lesion had a more or less reddish small opaque body attached. Both eyes had an incipient cataract with vitreous changes.

The lower portion of both legs from the knees downward was covered with thick infiltrated purplish to brown skin showing elevated nodules which appeared to contain dilated blood vessels and with large plaques of brownish pigmented crusts. More discrete lesions were present on the inner aspect of one thigh. On the left eyelid there was a pea-sized nodule of tumor tissue. On the right eyelid there was a purplish tumor 1 cm. long and 0.5 cm. wide; less definite involvement was noted on the left upper lid.

On Jan. 4, 1929, histologic examination of a specimen from the eyelid showed hemangiosarcoma of the lower lid, with implantation metastasis of the upper lid.

Urinalysis gave normal results.

Examination of the blood showed 4,020,000 erythrocytes, 9,400 leukocytes and 80 per cent hemoglobin. The results of the differential count were as follows: polymorphonuclear neutrophils, 59 per cent; large lymphocytes, 7 per cent; small lymphocytes, 25 per cent; mononuclears, 7 per cent; eosinophils, 2 per cent. The erythrocytes and platelets were normal. The sugar content of the blood was 50 mg., and the nonprotein nitrogen content, 26 mg., per hundred cubic centimeters.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ, New York: It is of interest to note that one of these patients was born in Ireland. The disorder usually appears in natives of the southern part of Europe.

ENDOTHELIOBLASTOMA RESULTING FROM TRAUMA. Presented by DR. JOHN G. DOWNING, Boston.

F. K., a man aged 42, an American, stated that while he was riding in a wagon in October 1918, a shell exploded nearby, killing the horses and rendering him unconscious. He regained consciousness at the Fifty-Second First Aid Station and found his neck, face and shoulder bandaged. When the dressings were removed the left side of his face and neck and the left shoulder were covered with crusts and serous fluid. The abrasions healed readily, but the area on the shoulder always showed signs of injury. Since that time his neck and shoulder have always felt

stiff, and occasionally pain is experienced on motion. About three months after the injury the patient noticed a deep swelling on the left side of his neck. This swelling continued to increase in size, and gradually red and blue spots and nodular swellings began to appear all over the injured area. Recently those on the left side of the face and neck have been growing quite rapidly and the patient has noticed that when he awakens the left eye is completely closed by swelling of the surrounding tissues. He feels that vision in this eye is poorer than previously.

The patient is well developed and well nourished and presents no abnormality except in the integument of the left side of the face and neck and of the left shoulder. On first inspection the impression is that the skin has been recently traumatized and shows ecchymotic spots, swelling and apparent hematomas. On closer examination these ecchymotic spots, which are numerous on the anterior and posterior aspects of the upper portion of the chest and on the entire shoulder region, are seen to be numerous punctate telangiectases which do not disappear on pressure. The left side of the neck is definitely swollen. The left half of the circumference of the neck measures 23.3 cm., whereas the right measures 21.4 cm. On palpation the left side has a more or less spongy feel. The swelling is irreducible, and the skin over the involved area is covered with numerous bluish, slightly infiltrated papules which do not fade on pressure. They vary in size from 2 to 5 mm. They are round or multilobular, and some are distinctly elevated and nodular. Behind the left ear is an irregular blue swelling 2 cm. long surrounded by bright red spots each the size of a pinhead. On the left side of the head the hair is sparse. Examination of the eyegrounds gave negative results, and roentgenograms of the skull showed no abnormalities. Two Wassermann tests of the blood were negative. New lesions are constantly appearing. The patient becomes aware that one is going to appear by the burning sensation which heralds them. When he is tired or attempts to lift a heavy object the swelling becomes more prominent. Two of these new growths were removed from the left side of the forehead, one by surgical procedure and the other by electrocoagulation. Since these operations were performed the swelling of the eyelids in the morning has become less noticeable.

The specimen examined consisted of an elliptic section of the skin from the forehead measuring 2 by 1 by 0.5 cm. In it there was a soft purplish nodule about 1 cm. in diameter. Microscopically a cross-section through the purplish nodule showed epidermis, corium and a small amount of the underlying striated muscle. Hair follicles, sebaceous glands and coil glands were present. The tumor was seen to surround and invade these various structures.

This tumor was composed of dilated spaces lined with endothelium and containing red blood cells. In some areas the endothelium was stretched thin and appeared to be only one layer in thickness. In others it had proliferated so that it was five or six cells thick or was growing in papillary projections into the lumen of the vessel. These papillary projections were supported by a connective tissue stroma and showed a tendency to be subdivided into numerous small capillaries containing blood. The endothelial cells seemed larger than normal and contained acidophilic cytoplasm and lightly staining nuclei. Mitoses were present among these cells but were rare. The cavities varied greatly in size and shape; some were circular; others were irregular and lobulated. They ranged from 2 to several hundred microns in diameter. The tumor was distributed rather diffusely throughout the section but lay for the most part in the corium surrounding the coil and the sweat glands. It was seen to be invading the fat tissue in that area. At one point it was superficial, lying just below the epidermis. It had also penetrated down between the bundles of striated muscle in the deepest portion of the section. In several places it was seen to be growing in papillary projections inside the lumens of distended veins. Not much of the normal structure of the veins could be made out, but the stretched smooth muscle fibers of their walls remained.

This case is presented because of the rarity of the condition. It was previously reported (ARCH. DERMAT. & SYPH. **22**:414-422 [Sept.] 1930).

DISCUSSION

DR. SAMUEL E. SWEITZER, Minneapolis: The diagnosis as presented, I think, is not correct at present. A diagnosis of endothelioblastoma would require more dissemination with glandular enlargement and more signs of lymphoblastoma. My diagnosis is hemangio-endothelioma. I have looked up this subject and found that many such lesions are reported to have followed injury. The changes in hemangio-endothelioma are groups of endothelial cells with capillaries at one side of the lesions. These capillaries are not mature and do not contain circulating blood. The ordinary hemangioma has capillaries that contain circulating blood and are mature. In many of the cases of hemangio-endothelioma reported the lesions were similar to this one, but in some they involved quite a large area. In most of the cases the condition is not fatal. The lesions are all of a rather low grade of malignancy, which ordinarily is not fatal.

PELLAGRA. Presented by DR. C. GUY LANE, Boston.

M. R., an American girl aged 11 years, has an eruption of two years' duration involving the face, hands, feet and elbows. She was apparently in good health until two years ago. Since then about every six weeks she experienced "spells" in which there was acute loss of strength without loss of consciousness. About seven months ago she collapsed while walking and was put to bed and treated for chorea. Three months ago she complained of diplopia, occasional headache and occasional vomiting. A month ago a circular area of erythema was noted under her eyes. Two and a half weeks ago her physicians noted a jacksonian attack starting in her right hand, extending up the arm and then involving the entire right side of the body. This attack lasted for several minutes, and after it had subsided the patient complained of diplopia and dizziness. During the past two years she had had attacks of diarrhea.

There is an irregular flush involving the front of the face and fading off toward the cheeks. At the angles of the mouth and on the chin and left cheek are impetiginous lesions. The skin of the hands is dry and wrinkled and shows brownish pigmentation. The elbows, knees and left foot show similar involvement. Around the anus and extending to the vagina there is an erythematous eruption mottled with yellow. Coarse nystagmoid movements are noted; the tongue is smooth and shows a coarse tremor. There is intention tremor of the hands. The tendon reflexes are markedly increased.

The urine was normal. Examination of the blood showed 4,200,000 erythrocytes, 10,300 leukocytes, and 80 per cent hemoglobin. The differential count gave normal results. The stools showed nothing abnormal. The spinal fluid was normal. Analysis of the gastric content showed free acid 0 and combined acid 10.

Large doses of yeast and liver extract improved the cutaneous condition markedly. At present there is no diplopia.

DISCUSSION

DR. RALPH HOPKINS, New Orleans: I can only say that the vestiges of the lesions now present seem to me to conform perfectly to what would be expected in a similar stage of typical pellagra. In regard to the nervous element, I do not feel qualified to express an opinion. It occurred to me that possibly the pellagra may have been a sequence of some other disease and that it may have been due to the disinclination of the child to eat while she was suffering from that other disease and after that. I think that one should not be surprised to see severe and varied nervous symptoms in patients with pellagra.

DR. RICHARD S. WEISS, St. Louis: I have observed a large number of cases of pellagra, and this child presents a familiar type—the type that is encountered among the children of well to do families who have been spoiled and have been allowed to choose their own food. The cutaneous symptoms seem to me to be characteristic; the sharply circumscribed patches of dermatitis on the hands and forearms and a glazing of the edges of the tongue combined with the neurologic

manifestations are characteristic of pellagra. The child also had repeated attacks of diarrhea. Administration of vitamin B and a high caloric diet with red meat, liver and puree of beans will probably clear up the condition and may alleviate the nervous manifestations if no structural damage has occurred.

A Case for Diagnosis. Presented by Dr. C. Guy Lane, Boston.

M. M., a Canadian woman aged 23, has a cutaneous condition which has been present intermittently for five and a half months. She had swelling of the breast, which persisted for six weeks; then she was operated on for abscess, but no pus was found. The pathologist reported chronic mastitis. One week after operation (four months ago) there appeared on the left arm a large swelling with red blotches, accompanied by slight tenderness and muscular weakness but no pain. The swelling has persisted. Two weeks later a similar swelling appeared on the right upper portion of the back, lasting one week. During the following two months there were exacerbations and remissions of the swelling of the left arm. One month ago swelling appeared in the left side of the neck, extending over the entire face and resulting in marked puffiness of the lower eyelids, which has persisted. One week ago the patient experienced pain in the chest on exertion, deep inspiration and coughing.

There is marked edema of the eyelids, left cheek and lower portion of the left arm; the right scapular region is swollen.

The heart was slightly enlarged, with a presystolic murmur at the apex.

Examination of the blood showed 3,990,000 erythrocytes, from 12,000 to 18,000 leukocytes, and 70 per cent hemoglobin. The differential count gave the following results: polymorphonuclear neutrophils, from 45 to 56 per cent; lymphocytes, from 51 to 41 per cent; eosinophils, from 1 to 2 per cent. A catheterized specimen of urine was normal. The Hinton test was negative. A test with a 1: 5,000 dilution of tuberculin gave definitely positive results. An agglutination test with Brucella and a cutaneous test with Trichinella, a preparation containing 15,000 organisms being used, gave negative results. A roentgenogram of the chest showed enlargement of the heart consistent with rheumatic heart disease.

Examination of specimens of skin and muscle from the site of the swelling of the left forearm revealed changes consistent with dermatomyositis.

DISCUSSION

Dr. Clark W. Finnerud, Chicago: The manifestations suggest to me a condition described by Buschke several years ago in the German literature as scleredema adultorum.

A Case for Diagnosis (Poikiloderma Atrophicans Vascular?). Presented by Dr. J. H. Swartz, Boston.

Mrs. S. B., a housewife aged 42, on her first admission in 1928 gave the following history: Twenty years ago there developed on the right forearm a small red and slightly pruritic area. Six months later a similar area appeared on the left upper portion of the anterior aspect of the chest, extending downward over the breasts, abdomen and genitalia and also involving the extremities and back. This eruption was more pronounced in the early part of the spring, and the skin was often scaly and dry. Examination at that time showed a short moderately obese woman who presented no abnormalities other than the cutaneous condition. The entire body was covered with a macular eruption of brownish or dull red macules ranging from 1 to 4 mm. in diameter. The creases of the body were most densely covered and pigmented. The breasts and extremities were least involved. The skin was dry and scaling.

The patient was seen again in 1930. At that time she showed many areas of hyperpigmentation. On the abdomen were many pinpoint areas of atrophy. About the elbows and upper portion of the forearm was a fine capillary dilatation with poikiloderma-like changes. The skin was thin and dry.

When the patient was seen in 1935, the pigmentation and atrophy were increased. Some of the areas exposed to the sun were free from involvement. Consultation with an endocrinologist revealed no basis for the lesions.

Examinations of the urine and blood, including chemical as well as serologic examination of the blood, gave negative results.

Two biopsies were made. On March 28, 1930, a specimen from the right elbow and one from the abdomen just below the costal border showed atrophic skin. On Dec. 30, 1935, the pathologic report was chronic inflammation with hyperpigmentation.

DISCUSSION

Dr. E. A. Oliver, Chicago: I believe that this patient's condition should be classed with the group of diseases that are called poikiloderma-like. She has some of the symptoms of poikiloderma, but, as in many of the cases which have been recorded in the transactions of the Chicago Dermatological Society, the symptoms do not quite correspond with those originally described by Jacobi. There are some interesting features in this case. There are sclerodermatous plaques on the sides of the legs and of the neck. The edema and erythema often seen about the eyelids in cases of real poikiloderma are lacking.

Oppenheim has divided poikilodermatomyositis into three main types: (1) the type described by Jacobi and by Petges and Clijat; (2) a congenital type with nevoid cutaneous changes, and (3) poikiloderma occurring as a terminal phase of a great variety of cutaneous diseases. I think that in this case the condition belongs in the latter group.

Dr. Fred Wise, New York: Most dermatologists frequently observe conditions of this kind, and, of course, the manifestations are interesting because of the lack of knowledge concerning the etiology. Various associated conditions may occur. One is the Cushing syndrome, pituitary basophilism; another is pathologic disturbance referable to the adrenal glands. In some of the patients who are followed up for a year or more much more serious conditions, such as lymphoblastomatous or lymphopoietic diseases, appear. My co-workers and I have a neurologist examine patients with these conditions for Cushing's syndrome or other endocrine disturbances. Frequently the report is negative, but we have the patient come back twice a year for further check up.

Pseudoxanthoma Elasticum; Angioid Streaks of the Retina. Presented by Dr. J. H. Swartz, Boston.

M. C. V., a woman aged 29, states that since July 1935 she has noticed gradual loss of vision of the left half of the right eye; she sees only the right side of an object. There are no spots in front of the eyes, but occasionally there is diplopia. The left eye is normal. Her chief complaint is sudden loss of vision.

The patient underwent a mastoidectomy in 1926. A goiter was removed in 1929 because of nervousness, loss of weight and perspiration; these disturbances cleared up after the operation. The exophthalmos cleared up four months after the operation. The patient had rheumatic fever in 1930.

There are discrete yellowish areas the size of a small pea on the lateral aspects of the neck. Vision is 20/30 in one eye and 20/20 in the other. Examination for thyroid disturbance revealed no evidence of hypothyroidism or tetany. A tremendous number of angioid streaks are present in both retinas.

The basal metabolic rate was —10 per cent. The urine was normal. The Wassermann reaction was negative. Roentgenograms of the skull showed no evidence of Paget's disease. The calcium content of the serum was 10.65 mg. per hundred cubic centimeters; the phosphorus content was 3.92 mg., and the phosphatase content, 3.52 units.

A section is presented.

DISCUSSION

Dr. Clark W. Finnerud, Chicago: This patient shows angioid streaks of the retina associated with pseudoxanthoma elasticum. Montgomery recently empha-

sized the fact that either of these manifestations may occur alone or the two may be present together. In the group of cases which Dr. Nomland and I are reporting (ARCH. DERMAT. & SYPH., to be published) we have incorporated all three of the possibilities. The ocular condition has not yet been studied histologically, and hence the relationship to the cutaneous condition is not yet understood. My co-workers and I have been impressed for some time with the fact that the marked blue staining observed in degenerated elastic tissue stained with hematoxylin is suggestive of calcium infiltration. We have been able to prove that the calcium content of the skin is markedly increased in this condition and that the calcium is present in the form of calcium phosphate. It is possible that similar changes will be demonstrated in the related retinal disturbance.

DR. J. H. SWARTZ, Boston: I remember talking to an ophthalmologist, Dr. Terry, who stated that Dr. Verhoeff has studied the pathology of angioid streaks. Dr. Terry reported four cases, in three of which Paget's disease was also present and in one of which streaks and pseudoxanthoma elasticum were observed.

DR. FRED D. WEIDMAN, Philadelphia: A discussion similar to this came up at a meeting of the Philadelphia Dermatological Society (ARCH. DERMAT. & SYPH. **35**:348 [Feb.] 1936) when Dr. Greenbaum presented a patient with this association of ocular and cutaneous lesions. At that time I was contradicted when I stated that angioid streaks had not yet been examined histologically. However, further inquiry into the results of the reputed (and only) histologic examination showed that there was not any certainty that the lesions examined were really angioid streaks. The lesions had not been recognized clinically; it was only after removal of the eye from the body that they were observed, and appearance in an excessively vascular structure such as the retina can change remarkably after such removal. I am inclined to agree with Dr. Finnerud that still the eyes have not been examined histologically as to angioid streaks.

For dermatologists the point of interest in those streaks is whether there is an excess of elastic tissue analogous to that in the skin. When that is ascertained it will be an open question whether the elastic tissue has undergone a fatty or perhaps calcareous change which might impart a more or less yellow color which may be characteristic.

DR. H. E. MICHELSON, Minneapolis: Dr. Montgomery in his article on pseudoxanthoma elasticum discussed the case to which Dr. Weidman referred. The complete description and the arguments pro and con will be found there.

OSTEOHYPERTROPHIC VARICOSE NEVUS. Presented by DR. JOHN G. DOWNING, Boston.

W. W., an electrician aged 37, was originally seen because of a fungous infection of his skin. Examination revealed an abnormality of the left side of his body. The left side of his face, especially the cheek, was considerably larger than the right. Examination of the buccal membrane revealed a distinct bluish tinge. The left hand and arm were considerably larger than the right. The left leg showed no marked difference except for a slight tendency toward a limp. The patient stated that this abnormality had been present since birth; in boyhood it was so marked that his companions called him "Limpey" because he was so lopsided. As he grew older the difference in the two sides of his body became less marked, and aside from the fact that he had an occasional severe attack of hemorrhoids his general health had been excellent. The patient is married and has two children; his wife has had no miscarriages.

The patient is well developed and well nourished. His weight is 135 pounds (61.3 Kg.); his height, 5 feet and 7½ inches (172 cm.). The temperature is normal. There are no ocular abnormalities and no evidence of disease. Between the eyebrows there is an area of superficial dilated blood vessels, 1.5 cm. square. The body shows a widespread superficial vascular nevus which is for the most part

of the diffuse cutaneous capillary type, although here and there is seen a hemangiomatous nodule. There is a varicocele on the left leg, and marked varicose veins are present on the entire left leg.

The Wassermann test of the blood and urinalysis gave negative results.

This man presents the three essential characteristics of this condition: bony enlargement, nevus and varicosity. The soft tissues show a true hemihypertrophy. The patient is presented because of the rarity of the condition.

DISCUSSION

DR. V. PARDO-CASTELLO, Havana, Cuba: Parkes-Weber was the first dermatologist to recognize this condition, and he reported a number of cases under the name hemangiectatic hypertrophy. The condition is typical, but the patients who exhibit it rarely come to a dermatologist. I have nothing to add except that the case is interesting. The syndrome consists of enlargement of the soft parts, enlargement of the bones, superficial angiomas and varicose veins. In practically all of these nevi there is arteriovenous communication. I have observed two cases of this condition, one in a young girl. In that case it was thought high voltage roentgen therapy might do some good. This treatment was employed, and the case was followed for two years, but there was no improvement. At first there seemed to be some reduction in the size of the affected member, but it was not lasting. Arteriography with thorium dioxide showed arteriovenous communication and numerous dilated collateral arteries around the femoral vessel.

Measurements of the Body

Roentgen Measurements		
Part of Body	Left, Cm.	Right, Cm.
Hand	21.2	19.0
Radius	23.7	22.5
Ulna	26.7	26.0
Humerus	32.2	31.3
Foot	16.5	16.1
Tibia	38.5	38.4
Fibula	37.9	38.0
Femur	38.7	39.3

Surface Measurements		
Part of Body	Left, Cm.	Right, Cm.
Head	27.0	27.0
Biceps	31.5	26.5
Midforearm	28.5	25.5
Spine to finger-tip	93.5	86.5
Chest nipple	45.5	42.0
Wrist to finger-tip	21.0	19.5
Thigh	52.5	53.0
Calf	37.0	37.5
Lower leg	88.0	90.0
Foot	28.5	27.5

DR. LEE MCCARTHY, Washington, D. C.: A patient with a similar condition was presented at a meeting of the Atlantic Dermatologic Society, and no one ventured a diagnosis. I am glad to witness this presentation and to hear the discussion.

DR. EARL D. OSBORNE, Buffalo: My co-workers and I observed a case of hypertrophy of the bones and arteriovenous communication, but there were no cutaneous manifestations.

ACRODERMATITIS CHRONICA ATROPHICANS. Presented by DR. JOHN G. DOWNING, Boston.

B. D., a Lithuanian woman aged 40, states that about seven years ago an eruption appeared on her right forearm, persisting and becoming worse in winter

when on exposure to cold the skin became reddish blue and cracked. At that time the patient was told that she was suffering from eczema. About three years ago her right hand became affected, especially during cold weather. At about that time she also noticed that she perspired only on her face and under her breasts, not on her hands or feet. Five months ago she noticed that her right leg and left arm were affected. At times the right hand became swollen, especially when the patient was doing some work. She had no pain, tingling or muscular weakness in the right arm. Recently the posterior part of her right leg began to pain and ache; she described the involvement as a "crawling sensation." She had no other cutaneous disease, except that about three years ago she suffered from a generalized urticaria. Otherwise her past history is irrelevant. General physical examination gave negative results. Her liver was 1 fingerbreadth below the costal margin.

The skin of the entire body is dryer than normal. The dryness is somewhat accentuated on the right arm and leg, which have a rather shiny, scaly appearance. This is most marked on the right arm, which is shiny and dry and presents a more or less reddish tinge accompanied by slight scaling, beginning just below the shoulder and becoming more marked downward toward the hand. There are atrophy, tiny pigmented spots and a fine telangiectasia, this condition being most marked on the dorsum of the hand. The right leg shows erythema with accentuation of the normal skin markings and a dry, wrinkled appearance. The left arm shows erythema, which varies from time to time. The left leg, except for slight dryness, is apparently normal.

A neurologic examination made while the patient was in the hospital gave negative results except for slight weakness of the right forearm.

The patient was observed at the Thorndike Memorial Hospital, the following data being obtained: Examination of the blood showed 5,690,000 erythrocytes, 7,900 leukocytes, and 101 per cent hemoglobin (Sahli). The differential count revealed 85 per cent polymorphonuclear neutrophils, 8 per cent lymphocytes, 6 per cent mononuclears and 1 per cent basophils. The Kahn test and urinalysis gave negative results. The basal metabolic rate was —16 per cent.

Roentgenograms of the chest showed chronic bronchitis; those of the arms and hands revealed no changes in the bones.

Biopsy showed atrophy of the epithelium and corium. The latter was diffusely and somewhat sparsely infiltrated with plasma cells and lymphocytes. No hyperkeratosis was present. The changes were not specifically diagnostic.

Dr. H. H. Merritt, visiting neurologist, made the following note: "There is some weakness of the muscles of the shoulder girdle. The cutaneous disorder may be related to the vegetative nervous system or may represent a beginning myopathy."

The results of intradermal injections of histamine and epinephrine did not deviate much from the normal reactions: 1. When 0.02 cc. of a 1:2,000 solution of histamine hydrochloride was injected intradermally in the dorsum of the right and left arm 3 inches (7.5 cm.) above the wrist, the wheal and flare on the right were slightly larger than the reaction on the left. The bleeding from the needle trauma was more profuse, and reactions appeared more quickly on the right than on the left side. 2. When 0.1 cc. of a 1:1,000 solution of epinephrine hydrochloride was injected 9 cm. above the wrist on the dorsum of both arms there resulted a blanching centrally with a flare peripherally, the width of the flare being the same as that of the reaction to histamine. The blanching was less distinct on the right but extended over a larger area. The blanching on the right seemed to follow definite pathways, probably lymphatics, and extended 6, 4 and 4 cm., respectively, in three distinct pathways. On the left the blanching was more localized and intense, and extended up the arm for 2.5 cm.

Skin temperatures were obtained over similar areas of the right and left hands, fingers and arms by means of a thermocouple. The readings were essentially the same on the two sides and were within normal limits.

Measurement of the skin resistance showed the resistance in the two arms, hands and fingers to be essentially the same and within normal limits.

Determinations of the flow of blood carried out by means of the Landis test gave results which were within normal limits in the involved and in the normal extremity. This test consists of immersing one extremity (the left leg was immersed in this case) in warm water kept constantly considerably above room and body temperature. Then, by means of a thermocouple, skin temperatures are determined on the opposite extremity. Normally, vasodilatation resulting from the heat takes place in all the extremities, an elevation of temperature resulting. If there is arterial spasm due to a pathologic vasomotor reaction, vasodilatation does not take place, and the temperature does not rise.

Whereas there was sweating of the normal leg, arm, abdomen and face, there was little sweating of the affected extremities as a result of the Landis test. This was considered abnormal.

Direct examination of the capillaries of the fingers by means of a microscope showed them to be normal.

This case is presented because of the rarity of the disease, and suggestions for therapy are requested. The case has been presented at the last meeting of the Atlantic Dermatological Society.

CLEVELAND DERMATOLOGICAL SOCIETY

H. G. MISKJIAN, M.D., *President*

March 26, 1936

J. R. DRIVER, M.D., *Reporter*

DERMATITIS VEGETANS. Presented by DR. H. N. COLE and DR. J. R. DRIVER.

Mrs. M. B., a physician's wife aged 22, had always been in good health until the summer of 1934, when she weighed 130 pounds (59 Kg.). Since then she has lost 30 pounds (13.6 Kg.). Half of this weight was lost during the past five months. In July 1934 she suffered from persistent diarrhea of unknown cause. In August 1934 she was treated for cystitis. There was no evidence at that time of tuberculosis of the bladder or kidneys. In August 1935, after two teeth were extracted, there developed on the lips "blisters" which later became crusted. The lips were treated with roentgen rays, and temporary improvement resulted. In October 1935 the patient shaved the axillary hair and immediately thereafter applied a deodorant, dew. A week later "blisters" appeared in the axillary fossae; these were followed by crusted lesions. In six weeks the process had cleared up and the hairs had grown out. Again the patient shaved the axillary hair, and two weeks later, in January 1936, new crops of "blisters" appeared. These were followed by the lesions the patient now exhibits. The involved areas have been treated by another physician with roentgen rays; a total of 2 skin units of radiation has been given. Recently a few crusted lesions have been noted on the scalp.

In each axillary fossa there is a large, well demarcated, irregular, dusky red, warty papillomatous patch. Vesiculopustules from the size of a pinhead to that of a pea are scattered over these vegetating areas. The borders are raised. There are several smaller but similar patches just beyond the large patches. On the scalp are some crusted lesions. On the legs are faint pigmentary remains of a vesicular eruption which was diagnosed in 1935 as dermatitis venenata. There are crusted lesions on the lips. The blood pressure is 130 systolic and 85 diastolic; the temperature ranges from 37 to 37.5 C. (98.6 to 99.5 F.). There are no clinical signs of involvement in the thorax or abdomen. The mucous membranes are pale.

Roentgenograms of the chest disclosed no abnormalities. Urinalysis gave negative results. Examination of the blood showed 3,600,000 red and 11,000 white cells. The results of the differential count were as follows: 47 per cent poly-

morphonuclears, 37 per cent large mononuclears, 3 per cent mononuclears, 12 per cent eosinophils and 1 per cent basophils. Examination of the stools showed a 4 plus reaction for occult blood, many red and white blood cells and many gram-negative bacilli and gram-positive cocci in chains; no amebas were observed. The urea nitrogen content of the blood was 8.3 mg., and the sugar content was 83 mg., per hundred cubic centimeters. The Wassermann reaction of the blood was negative. Smears of contents of a vesicle showed no amebas or mycotic organisms.

Neurologic and ophthalmologic examinations gave negative results.

The results of histologic examination were reported as follows: There were circumscribed intra-epithelial collections of leukocytes, papillomatous epidermal hyperplasia with elongation of the papillary bodies, edema of the papillae and perivascular lymphocytic infiltration. Throughout the corium were diffuse and dense infiltrations of an exudate rich in eosinophils.

Treatment has consisted of compresses of a 1:6,000 solution of mercury bichloride applied twice a day.

DISCUSSION

DR. EMERSON GILLESPIE, Canton, Ohio: The associated bullous lesions which have appeared on the lips cause me to favor a diagnosis of pemphigus vegetans.

DR. H. J. PARKHURST, Toledo, Ohio: The possibility of monilial infection should be considered. I believe that the lesions in the mouth, axillae and scalp could be explained by such an infection, in spite of the fact that examinations for fungi have given negative results so far.

DR. R. E. BARNEY: I too had the impression that the condition might be a fungous infection. The granulomatous appearance of the lesions, both histologically and clinically, suggest the possibility of blastomycosis or perhaps tuberculosis verrucosa cutis. The fact that the patient has lost considerable weight would make one a little suspicious.

DR. E. W. NETHERTON: I should not agree to a diagnosis of tuberculosis in this case. However, the possibility of fungous infection should be kept in mind, and further studies should be made.

DR. J. R. DRIVER: In spite of the fact that this patient has been in the hospital for several days and that numerous studies, including examination for microorganisms, biopsy and roentgen examination of the chest, have been made, my co-workers and I have not been able thus far to make a positive diagnosis. I do not believe that the condition is a vegetating type of pemphigus. The patient is not ill as one would expect her to be if she had that disease. The eruption in many respects resembles a kerion type of fungous infection, and, as is usually the case, it is impossible to demonstrate the organisms. This may explain the failure along this line. The disease is much more resistant to treatment than one would expect a pyoderma to be. However, this case is presented as one of dermatitis vegetans, as no etiology has been established.

CHRONIC BULLOUS ERUPTION. Presented by DR. R. O. RUCH, Lima, Ohio.

O. L., a boy aged 3 years, whose parents state that there is no history of cutaneous disorders, three days after birth exhibited a bullous eruption about the ankles. From time to time the eruption became much more extensive, and once, when the patient was 1 year old, it almost disappeared. At present there is a generalized erythematous bullous eruption involving especially the chin, palms, soles and knees. The toe-nails are markedly thickened. The bullae are rather tense and vary in size from that of a pea to that of an olive. The Nikolsky sign is positive. The lesions are tender on palpation, and in some instances crusts have formed on the base of former bullae.

The hemoglobin content was 90 per cent; there were 4,500,000 red and 12,700 white blood cells. The differential blood cell count was normal.

Treatment has consisted of applications of solution of potassium arsenite for a period of two months one year ago. Baths of potassium permanganate and application of various lotions have been used without any beneficial effect.

A biopsy has not been performed.

DISCUSSION

DR. C. L. BASKIN, Akron, Ohio: I have had a patient, a child, with a similar eruption which had been present for about two years. The process was not as severe as in this patient. The palms and soles were free from lesions. I treated her with methyl salicylate internally, and the eruption disappeared at the end of three weeks.

DR. H. J. PARKHURST, Toledo, Ohio: The possibility of pemphigus, of dermatitis herpetiformis and of epidermolysis bullosa should be considered. The general health of the child seems to be good, which would be against a diagnosis of pemphigus. There is not enough pigmentation to justify a diagnosis of dermatitis herpetiformis. Therefore, by elimination, I favor that of epidermolysis bullosa.

DR. L. J. CARSON: The process is too extensive to be epidermolysis bullosa. I favor the diagnosis of dermatitis herpetiformis.

DR. E. W. NETHERTON: Against the diagnosis of epidermolysis bullosa is the fact that this disease seems to be too extensive and develops in crops, producing almost a generalized distribution. It would be hard to explain how trauma could produce so many lesions in so many different areas. I should not make a diagnosis of either erythema multiforme or pemphigus. I favor most the possibility of an allergic condition, and I suggest that the studies for foci of infection be made.

ERYTHEMA MULTIFORME DUE TO PHENOBARBITAL. Presented by DR. G. W. BINKLEY.

F. M., a man aged 45, from the City Hospital, was admitted to the tuberculosis division three weeks ago because of pulmonary tuberculosis. He had been given 1½ grains (0.086 Gm.) of phenobarbital every night since admission. On March 22, 1936, an eruption consisting of red configurate and iris-shaped bullous and edematous lesions appeared on the trunk, legs and ankles. The upper portion of the back and the shoulders are most markedly involved. On the legs are numerous clear, tense bullae which apparently developed on normal skin. There is no surrounding inflammation. There is no history of ingestion of phenobarbital before admission to the hospital.

DISCUSSION

DR. E. W. NETHERTON: Cutaneous eruptions due to phenobarbital are rather common. The drug is used extensively, and the fact that these eruptions can occur is not known by many physicians. It is my opinion that the drug is prescribed too freely.

DR. H. J. PARKHURST, Toledo, Ohio: I agree with Dr. Netherton. Owing to the extensive use of this drug I have seen many patients with such eruptions at the County Hospital in Toledo, Ohio. In many cases the lesions are of a morbiliform and scarlatiniform type.

DR. JOHN E. RAUSCHKOLB: The bullous type of eruption following ingestion of phenobarbital is not so common, in my experience, as the erythematous type.

DR. M. J. GIBANS, Akron, Ohio: I have recently seen a patient who had an extensive bullous eruption around the mouth resulting from the ingestion of luminal.

DR. J. R. DRIVER: I have observed a case recently in which a diagnosis of erythema multiforme was made. The etiology was obscure. After a period of time it was noted that fresh attacks of the eruption appeared after the patient had taken phenobarbital, and when the use of the drug was stopped there was no further trouble.

HIDRADENITIS AXILLARIS (VERNEUIL). Presented by DR. G. W. BINKLEY.

L. J., a Negro boy aged 10 years, from the City Hospital, was a patient in the hospital at the age of 15 months, at which time he had an eruption limited

to the axillae which had been present since he was 1 year old. At that time the skin of the axillae presented a thickened appearance, hyperpigmentation and small follicular abscesses and sinuses discharging considerable amounts of pus. The process was extremely resistant to all types of treatment, including antiseptic applications and roentgen therapy. The eruption finally cleared up in about one year. There have been recurrences from time to time, and the patient has been hospitalized on several occasions, the last admission being in January 1930. The present attack has lasted for several months, and the patient now presents sharply circumscribed thickened, indurated areas of approximately the size of a silver dollar in the axillae. The surface shows some scaling, hyperpigmentation and a small amount of crusting resulting from dried seropurulent discharge.

The results of histologic examination were reported as follows: The epidermis was normal. The corium showed relatively dense bundles of connective tissue. Just below the epidermis were many well circumscribed clumps of leukocytes. The microscopic abscess extended down to, and around some of, the groups of coil glands, and in places sweat glands were destroyed. The great majority of the coil glands, however, showed little involvement.

Improvement has resulted from application of a lotion of bismuth tribromphenate and zinc oxide and warm compresses of solution of potassium permanganate.

DISCUSSION

DR. R. E. BARNEY: In the differential diagnosis one would have to consider also the possibility of a kerion type of trichophytid. The histologic changes were minimal.

DR. J. R. DRIVER: My co-workers and I have seen this patient in our clinic on various occasions over a long period of time. The process is extremely chronic. In 1930 histologic examination showed inflammatory reaction, especially about the sweat glands, with some abscess formation and sinuses. Extensive studies from the standpoint of dermatomycosis have all given negative results. On previous admissions autogenous vaccines made from cultures of the pus have been of considerable value. It is quite certain that the condition is hidradenitis axillaris of Verneuil.

SARCOID-LIKE TUBERCULOSIS OF THE SKIN. Presented by DR. G. W. BINKLEY.

S. W., a Negro aged 33, from the City Hospital, was presented before the society on Oct. 17, 1929 (ARCH. DERMAT. & SYPH. **21**:500 [March] 1930), on Feb. 25, 1932 (ARCH. DERMAT. & SYPH. **26**:586 [Sept.] 1932), and on Sept. 22, 1932 (ARCH. DERMAT. & SYPH. **27**:343 [Feb.] 1933). The diagnosis was multiple sarcoid-like lesions of the skin.

The patient has recently been readmitted to the hospital, being referred to the tuberculosis division. He now presents a complete regression of the extensive eruption. He has an advanced degree of tuberculosis of the lungs associated with cavitation, and smears of the sputum contained tubercle bacilli.

DISCUSSION

DR. JOHN E. RAUSCHKOLB: When the patient was previously admitted to the hospital extensive laboratory investigations were made. Tests with both animal and human tuberculin gave negative results in dilutions as low as 1:100. Inoculations of guinea-pigs and chickens with material from the cutaneous lesions gave negative results. Physical examination and examination of the sputum gave negative results. Roentgenograms of the chest showed no abnormalities. The patient had a true anergy to tuberculin. While it has always been suspected that he had tuberculosis, the present pulmonary symptoms are the first definite evidence of that disease.

DR. J. R. DRIVER: It is interesting to see this patient again now that there is evidence of tuberculosis. Why the cutaneous lesions should regress completely after the active flare-up of tuberculosis of the lungs is difficult to explain. It will be recalled that in the case reported by Dr. Weidman and Dr. Klauder there also was evidence of tuberculosis of the lungs at autopsy.

H. G. MISKJIAN, M.D., *President*

April 23, 1936

J. R. DRIVER, M.D., *Reporter*

A CASE FOR DIAGNOSIS. Presented by DR. R. E. BARNEY.

H. W., a man aged 48, noticed about eighteen months ago that the right side of the lower lip was red and swollen. Subsequently small blisters developed, and the lesion was interpreted as herpetic. It persisted, however, for over a year, gradually becoming larger, and during the past six months it has become progressively worse. About two months ago the lower jaw became involved, and the four lower incisors were then lost. Sinuses formed on the chin and lip and discharged pus.

At present there is a diffuse nodular eruption on the right half of the lower lip, extending from the vermilion border to the ramus of the mandible. These nodules vary in size from that of a small pea to that of a walnut and seem to be fused. They are deeply seated, hard and painless on palpation. Several of the nodules present intercommunicating sinuses, from which a yellowish watery discharge can be expressed. The lower gum, at the site of the missing teeth, presents a necrotic ulceration, and rough bone can be demonstrated with a probe. There are olive-sized painless firm cervical nodes on both sides. The Wassermann reaction of the blood was negative. The blood cell counts and differential cell counts were within normal limits. Repeated examinations of smears for Actinomyces gave negative results. Stained smears revealed gram-positive cocci, gram-negative bacilli and numerous spirochetes. Roentgen examination showed considerable destruction of the right mandible, extending back to the anterior border of the second bicuspid and anteriorly to the central incisors. Four biopsy specimens have been removed at different times, but the microscopic examination has revealed only chronic inflammatory tissue. Treatment has consisted of local antiseptic applications and oral administration of potassium iodide. No improvement has been noted.

DISCUSSION

DR. J. R. DRIVER: Clinically the process resembles actinomycosis more than anything else. The possibility, however, of this condition's being secondary to an osteomyelitis of the jaw would have to be considered. Further search for Actinomyces might prove successful.

NOTE.—At the September meeting Dr. Barney reported that further search for Actinomyces had been unsuccessful, that the process had become more extensive and that it had shown no response to any form of therapy. He stated that in his opinion the process was secondary to dental abscesses.

SUBACUTE DISSEMINATED LUPUS ERYTHEMATOSUS AND PULMONARY TUBERCULOSIS. Presented by DR. R. E. BARNEY.

A. C., a man aged 39, presents an eruption on the hands and face of six months' duration. The eruption involves the bridge of the nose and extends onto the cheeks in a butterfly configuration. It is subacutely inflammatory, scaly and sharply demarcated. The scales are sparse and closely adherent. The sebaceous

orifices on the nose are dilated and plugged with horny masses. There is some edema of the involved areas, and on close examination areas of telangiectasia can be seen. The neck and the lobes of the ears are involved to a less extent. The flexor surfaces of the fingers and the adjacent surfaces of the palms as well as the dorsal surfaces of the fingers are involved. The soles show a moderate degree of involvement.

A roentgenogram of the chest revealed pleurisy and evidence of healed hilar tuberculosis on the right side and tuberculous scarring in the apex of the left lung. Some improvement has been noted after injections of gold sodium thiosulfate and local application of an ointment containing sulfur and salicylic acid.

LUPUS ERYTHEMATOSUS; CHRONIC PULMONARY TUBERCULOSIS. Presented by DR. E. W. NETHERTON.

L. K., a man aged 55, had pneumonia in 1905. Two years later pulmonary tuberculosis developed, and the patient was hospitalized in a sanatorium for twenty-one months. About eighteen months ago a small red spot developed on the left cheek; this gradually enlarged, resulting in a scaly area. This lesion extends from just below the eye to the ala of the nose and involves the lower and anterior portion of the cheek. It is erythematous, fairly well defined, slightly raised and edematous. Palpation demonstrates some infiltration. The central portion of the lesion is atrophic and covered with a yellowish seborrheic type of scale. The border of the lesion is more erythematous, and the follicles are dilated. There is suggestive clubbing of the fingers.

A roentgenogram of the chest showed the trachea displaced toward the right side. The cardiac outline was obscured. The pleura was thickened over the left lung, and the left portion of the diaphragm was normal but obscure. The right lung showed an extensive fibrous and thickened pleura over its entire surface, and small cavitation was present in the middle of the lung. There were some calcified nodes in the upper lobe.

A histologic examination showed hyperkeratosis with hyperkeratotic plugs in the follicles. There were edema and fragmentation of the collagen fibers in the corium and papillary layer. There were areas of almost pure cellular infiltration in the corium around the coil glands and hair follicles, extending into the subcutaneous fat. There were no tubercles, giant cells or areas of necrosis.

A test with a 1:5,000 dilution of tuberculin was positive and produced a focal reaction in the lesion on the cheek.

PATHOMIMESIS. Presented by DR. H. G. MISKJIAN.

T. B., a housemaid aged 20, underwent an appendectomy in 1933. A year later a laparectomy was performed for the freeing of adhesions. Since that time the patient has complained of abdominal pain, poor appetite, sleeplessness, frontal headache and recurrent spasms of the muscles of the right side of the face and right extremities; she states that periodic remissions occur. She was hospitalized and treated for ovarian dysfunction by administration of theelin. She was discharged from the hospital on March 26, 1936, and returned on April 6, presenting cutaneous lesions consisting of large circular or irregular areas on the face, arms and trunk. The lesions are covered with a dry, brownish, parched-looking epidermis; they have sharply defined borders, and there is a surrounding inflammatory reaction in the skin. In a few of the lesions some impetiginous crusts are present. The areas in some places resemble "matburns." New lesions have appeared from time to time, and older lesions have healed, leaving no scars. All the lesions are in areas which can be reached by the patient's hands. I made a diagnosis of self-inflicted lesions. I suggested that a lesion would appear on the cheek, which at the time was clear, and in three days the lesion did appear.

DISCUSSION

DR. H. G. MISKJIAN: This case is, without question, one of so-called dermatitis factitia, and I presented the patient with the idea of questioning the advisa-

bility of this term. Obviously in many cases in this category there is no dermatitis at all. Many of the lesions produced artificially are even gangrenous. The term *pathomimie*, used by Dieulafoy, seems to be much more acceptable, as it means simulation of disease or the mimic of disease. In my opinion the term should be adopted.

ACROSCLEROSIS OF SELLEI. Presented by DR. G. W. BINKLEY.

D. M., a Grecian housewife aged 41, from the City Hospital, has had four children; three are living and well. There is no history of any serious illness. Approximately thirteen years ago there developed swelling of the fingers associated with pain. The condition became worse in cold weather; when the hands and feet were immersed in cold water they became cyanotic and burning pain developed. For the past ten years the face, arms and legs have been involved. The patient appears to be somewhat anemic and presents a masklike facies. The skin of the face, forearms, hands, feet and legs is yellowish white and dotted with numerous matchhead-sized telangiectases. The nose is thin, and the nostrils are contracted. Radiating lines stand out from the lips and corners of the mouth. The skin of the face and forearms is thickened, firm and rubbery and when pinched is inelastic. The terminal phalanges of the digits of both hands are missing as a result of ulceration and atrophy. There are thick callosities over the tibial tuberosities of both knees, which are due to the patient's crawling since walking is frequently painful.

The Wassermann reaction of the blood was negative. A blood count revealed 4,900,000 red cells, 8,000 white cells and 80 per cent hemoglobin. The basal metabolic rate was zero. The calcium content of the blood was 10 mg.; the phosphate content, 7.1 mg., and the urea nitrogen content, 19.3 mg., per hundred cubic centimeters.

A roentgenogram of the hands showed absence of distal phalanges. There was, in addition, evidence of some destruction of the second phalanges of both hands.

Histologic examination of a section stained with hematoxylin and eosin showed hyperkeratosis. The epidermis was actually narrow, but because a peculiar budding-like acanthosis was present it seemed wider than it really was. The interpapillary pegs were avascular and stained dark red with eosin. No small blood vessels were seen, but deeper in the corium there were a few large, thick-walled vessels with narrow lumens. The sweat glands present were prominent, either owing to an increase in the actual number of coils or to the atrophy of the other tissues of the skin. They were definitely nearer the surface epithelium. Collagen stain showed dense intertwining bundles of connective tissue and absence of blood vessels.

DISCUSSION

DR. H. J. PARKHURST, Toledo, Ohio: This is the first case of this condition that I have observed in which the complete picture with telangiectasia, as described by Sellei, is present.

DR. J. R. DRIVER: This is a rare condition which could not be diagnosed as scleroderma. For example, the hidebound appearance is lacking; instead there is a rubbery inelastic feel to the skin. The blood supply does not appear to be diminished as much as in scleroderma. I agree with Dr. Parkhurst that the condition is acrosclerosis.

DR. G. W. BINKLEY: I have no suggestions to offer in regard to this case, but after a careful study of Sellei's work, as reported in the *British Journal of Dermatology and Syphilis* (**46**:523, 1934), I am convinced that this patient's condition is acrosclerosis. She has all the symptoms; the process is symmetrical, and it began on the hands and the face at the same time. This is one of the striking symptoms which differentiates this entity from scleroderma. Scleroderma occurs in a spotty distribution on different parts of the body and is entirely asymmetrical. The changes in this case are strictly symmetrical. The patient exhibits the masklike transformation of the face, and the skin of the face is not hard but

has a firm rubbery consistency. She has the vasomotor changes accompanied by pain in cold weather. Finally, this patient has the telangiectasia, pigmentation and loss of terminal phalanges (sclerodactylia). This disorder has been grouped with scleroderma, but since the symptoms, etiology, treatment and prognosis of the conditions are different, I am convinced that acrosclerosis should be recognized as an entity.

FOX-FORDYCE'S DISEASE. Presented by Dr. E. W. NETHERTON.

E. B., a woman aged 35, had measles, mumps and chickenpox when she was a child. Her menses began when she was 17 and have been regular, occurring every twenty-four days and lasting from three to four days. For the last fifteen months she has had an itchy eruption in the axillae and pubic region and has been unable to obtain any permanent relief. The pruritus is worse during the day; it does not interfere with her sleep. She is well developed but rather poorly nourished. She exhibits an eruption in the axillae consisting of round discrete small papules, many of which are follicular. Only a small amount of hyperpigmentation and a moderate loss of hair are noticeable in the axillae. The pubic area is involved to a much less severe degree. The breasts are poorly developed. There are an excessive growth of hair on the cheeks, chin and lips and a profuse growth of hair on the legs.

General physical examination gave essentially negative results except for the fact that the thyroid gland was enlarged.

A blood count revealed 3,900,000 red cells, 8,900 white cells and 76 per cent hemoglobin. The sugar content of the blood was 161 mg.; the urea nitrogen content, 48 mg.; the uric acid content, 1.6 mg.; the nonprotein nitrogen content, 50.4 mg., and the cholesterol content, 208 mg., per hundred cubic centimeters. The Wassermann and Kahn reactions of the blood were negative. Urinalysis gave negative results.

Microscopic examination revealed, in places, a slight amount of hyperkeratosis in the epidermis, especially in the orifices of the follicles. There was a moderate degree of acanthosis, and a slight amount of round cell perivascular infiltration was present in the upper part of the corium and in the papillary layer. There was also a mild lymphocytic infiltration around the coil glands. The coil glands showed a degenerative process consisting of dilatation, destruction of the glandular epithelium and, in places, débris within the degenerated coils.

A slight improvement in the pruritus followed the application of four superficial roentgen treatments.

DISCUSSION

DR. E. W. NETHERTON: I presented this case because of the evidence of endocrine dysfunction. In several cases of Fox-Fordyce's disease which have been presented before the society the marked evidence of pluriglandular disturbance was not present.

LUPUS ERYTHEMATOSUS OF THE MOUTH. Presented by DR. R. E. BARNEY.

M. K., a woman aged 37, states that about four years ago a painful ulcer developed on the left portion of the buccal mucous membrane. Subsequently the right portion of the buccal mucous membrane, the hard palate and the throat became involved. There have been periodic improvement and exacerbation, the latter occurring particularly at the time of the menses. At present the buccal mucous membrane on the right side presents bluish superficial erosions about 2 cm. in diameter. The borders show numerous fine radiating white lines which diverge peripherally. A similar but less marked process is present on the left side. The posterior half of the hard palate presents a similar picture, showing annular lesions the size of a pinhead and larger which have coalesced to give a mosaic appearance. There are no lesions on the skin. General physical examination gave negative results. The Wassermann reaction of the blood was negative. Blood cell counts and the urinalysis gave normal results.

Histologic examination showed merely chronic inflammatory tissue.

The patient has improved after receiving five intravenous injections of gold sodium thiosulfate, 25 mg. being given at each injection.

DISCUSSION

Dr. J. Edgar Fisher: From the appearance of the striation at the border of the lesions on the right cheek I favor a diagnosis of lichen planus.

Dr. C. L. Cummer: I agree with the diagnosis of lupus erythematosus.

Dr. H. J. Parkhurst, Toledo, Ohio: It is true that the lacy meshwork of the lesion in the right cheek is somewhat suggestive of lichen planus, but the central portion of this lesion and the other lesions are more characteristic of lupus erythematosus, and I agree with the diagnosis as presented.

LOS ANGELES DERMATOLOGICAL SOCIETY

Nelson Paul Anderson, M.D., *Chairman*

May 5, 1936

Thomas W. Nisbet, M.D., *Secretary*

Roentgen Ray Dermatitis (Superficial Epithelioma of the Bowen Type) Following Roentgen Examination. Presented by Dr. Moses Scholtz.

Mrs. C., aged 35, first noticed the lesion in July 1935. She had been treated for infection of the gallbladder by drainage, and several roentgenograms of the gallbladder had been taken in the dorsal position. When she was seen by Dr. Max Wolf, in July 1935, the lesion was superficial, exhibiting a violaceous, almost purple, center and a dull red periphery. A few days later it became raw and denuded. It healed over in about September 1935. Three weeks later it became dry, wrinkled and hyperpigmented in the center and depigmented at the periphery. Three months later the patch became infiltrated, parchment-like, shiny and yellow-white, resembling old marble, and the surface was seen to be traversed by fine pinkish vessels. Treatment consisted of application of mild ointment and ultraviolet irradiation. The general health at present is good.

DISCUSSION

Dr. H. C. L. Lindsay: I believe that there are some epitheliomatous changes in the lesion already.

Dr. Samuel Ayres Jr.: I agree with Dr. Lindsay that there is probably epitheliomatous degeneration. A biopsy should be made, and if possible the whole involved area should be removed with the cautery or the endotherm knife.

Dr. Stanley Chambers: The disorder is obviously a roentgen ray dermatitis with questionable malignant degeneration. If one is willing to believe that it is only a roentgen ray dermatitis without malignant degeneration, and if there is not proof to the contrary, I should suggest the use of the leaf of Aloe vera. My co-workers and I have discovered a large supply of this cactus, and the plant can be obtained through a local drug store.

Dr. Samuel Ayres Jr.: My co-workers and I have treated various types of ulcerations with Aloe vera in the last year. One woman had extensive roentgen ray dermatitis involving the back and other areas. She applied some cream which caused a dozen chronic ulcerations. From the appearance of her lesions it seemed that the only thing to do would be to remove them with cautery and to resort to skin grafts. We used Aloe vera, and the lesions disappeared in a few weeks.

Dr. Nelson Paul Anderson: I think this patient had some roentgenograms of the chest made a few years ago. Obviously only little radiation would be absorbed by the back. This condition seems to be a roentgen ray ulcer resulting from fluoroscopic examination and from exposure to roentgen rays when roentgen-

ograms of the gallbladder were made in 1934. The patient apparently had no trouble until about a year later. While the ulcer might heal and present an excellent result from treatment with the leaf of Aloe vera, I think that excision of the whole area would do away with the pain which the patient has and at the same time remove a potentially malignant area.

DR. MOSES SCHOLTZ: There is one point of interest in roentgen ray dermatitis produced by roentgen examination and not by roentgen treatment. It seems that roentgenograms are made indiscriminately, regardless of the number of exposures to which the patient is submitted. I think that this fact should be emphasized and called to the attention of the profession.

CONGENITAL ECTODERMAL DEFECT. Presented by DR. NELSON PAUL ANDERSON.

J. C., an American girl aged 4 years has an irrelevant family history so far as can be determined. This child is the second of three children. She was born normally at term. She is fairly well developed and exhibits rather sparse and scanty growth of hair. The nasal bridge is depressed and sunken, and the skin over it is somewhat shiny and glazed. Only four teeth are present, and these are irregular and deformed. On the forearms and on the lower portion of the legs are certain glazed, apparently depigmented areas which according to the mother are the only areas which ever sweat. Supernumerary nipples are present on both sides. The Wassermann reaction of the mother's blood as well as of that of the father, of the oldest child and of this patient is negative. A lumbar puncture was made when the child was 8 months old, and apparently the fluid was normal.

DISCUSSION

DR. H. C. L. LINDSAY: Marked hypothyroidism will produce lesions like those exhibited by this patient.

DR. MOSES SCHOLTZ: Irrespective of whether any special entity exists or not, I do not think one can separate the disorder from the nevoid type of lesion. It has been present from birth. It suggests an anemic linear nevus. There is absence of teeth and hair. The disorder is a marked congenital ectodermal defect.

DR. NELSON PAUL ANDERSON: I am sorry Dr. Goeckerman is not here tonight, because he was the first man in this country to observe this syndrome. The loss of eyebrows, the apparent saddle-back nose, the continuous rhinitis, the dental defects and the scanty hair are quite characteristic. The presence of supernumerary nipples such as this child exhibits is unusual. This patient has some sweat glands that function, but complete loss of the sweating function has been present in some of the cases reported. I am not familiar with any definite name that has been given to this syndrome. I think that the prognosis, as far as any benefit from treatment is concerned, is exceedingly bad. I do not know what to do for this patient except to tell the mother not to take her to physicians, for most of them will want to treat the child for congenital syphilis.

MANHATTAN DERMATOLOGIC SOCIETY

PAUL E. BECHET, M.D., *Chairman*

May 6, 1936

MIHRAN B. PAROUNAGIAN, M.D., *Secretary*

LUPUS ERYTHEMATOSUS DISSEMINATUS IN A GIRL AGED 9 YEARS. Presented by DR. ISADORE ROSEN.

W. T., a girl aged 9, was first seen at the New York Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Dec. 30, 1935, with an eruption of four months' duration.

On the bridge of the nose and adjacent areas on the cheeks and eyelids of both eyes was a typical butterfly eruption associated with marked erythema and some scaling. There were no dilated follicles and no atrophy of the skin. The eruption involved the skin of the backs of some of the fingers and around the elbows. Since December there has been a moderate improvement. The patient had had nine injections of a bismuth preparation.

DISCUSSION

DR. GEORGE C. ANDREWS: It is an unusually interesting case. I do not think there is any doubt about the diagnosis as presented.

DR. H. J. F. WALLHAUSER: I agree with the diagnosis, but on account of the acute onset, I feel we should not forget the presence of a possible focus of infection; a similar eruption under my observation was found to be due to a purulent appendix.

LUPUS ERYTHEMATOSUS DISSEMINATUS IN A CHILD. Presented by DR. HOWARD FOX.

D. S., a schoolgirl aged 10 years, has suffered from the present eruption for the past three and a half years. It involves the nose, cheeks, a typical butterfly configuration being present, and the dorsal aspect of the hands. The lesions are superficial, red, dry and fairly well defined and have not caused any subjective symptoms. At present there is a small amount of adherent branny scaling. Until a month ago the patches were entirely smooth. There have been frequent partial remissions after treatment with doses of 5 and 10 mg. of gold and sodium thiosulfate. The patient received a total of twenty-four injections. At no time did the eruption disappear entirely. It began originally after the patient suffered a sunburn, and it has always shown a tendency to be photosensitive.

A roentgenogram of the chest showed no evidence of tuberculosis, and tests with graded dilutions of tuberculin, a dilution as low as 1:5,000 being used, were negative. The patient is said to have had measles seven years ago. At present her general health is good.

DISCUSSION

DR. A. W. GRACE (by invitation): It would be interesting to ascertain whether there is any difference in the red cell sedimentation rate in the quiescent and in the active stage of the disease. It is reasonable to assume that increased activity of foci of infection would be reflected in an elevated sedimentation rate.

DR. PAUL E. BECHET: I think these disorders are interesting, particularly when they affect children. Their occurrence in children was formerly considered rare, but in the past ten years I have observed a marked increase in the number of cases of acute lupus erythematosus in young children, and I believe that the incidence is increased greatly by the custom of constantly exposing the body to the sun's rays in the summer. In order to increase the effects of exposure to the sun's rays these tots now wear bathing suits which practically cover only the trunk. There is a history of exposure to the sun's rays in Dr. Fox' case.

DR. HOWARD FOX: Lupus erythematosus in children is probably not as rare as has been generally supposed, although it is unusual for two cases of that disorder to be presented at the same meeting. I have records of a number of cases, the youngest patient having been 5 months old. I shall try to carry out Dr. Grace's suggestion regarding the sedimentation test of the blood.

A CASE FOR DIAGNOSIS (KERATOSIS PILARIS?). Presented by DR. J. FRANK FRASER.

W. T., a boy aged 14, was presented before the New York Dermatological Society on April 28, 1936. The case was presented under the title "A Case for Diagnosis (Dermatitis Seborrhœica [Follicular Type]?"). A microscopic examination was reported to show a mild chronic dermatitis. The lesions have been

present for about four months and are reddish brown, from round to oval and from the size of a dime to that of a large coin. They are follicular and in some respects resemble a keratosis pilaris type of eruption.

DISCUSSION

DR. H. J. F. WALLHAUSER, Newark, N. J.: I suggest the diagnosis of lichen pilaris seu spinulosus. The disorder, as described by Crocker, consists of keratotic papules located about the follicles and of spiny projections of horny epithelium arranged in patches.

DR. GEORGE M. MACKEE: Several keratotic follicular diseases have to be considered. I am inclined to agree with the diagnosis presented by Dr. Wallhauser.

DR. FRED WISE: I agree with the diagnosis suggested by Dr. Wallhauser.

DR. PAUL E. BECHET: The follicles are not inflamed but are raised and spiny. I agree with the diagnosis made by Dr. Wallhauser.

DR. J. FRANK FRASER: I thank Dr. Wallhauser for his suggestion and accept his diagnosis.

TERTIARY SYPHILIS (LATE). Presented by DR. ISADORE ROSEN.

F. F., a man aged 28, was first seen at the Skin and Cancer Unit of the New York Post-Graduate Hospital in April 1936, with an eruption of five months' duration.

In 1931 the patient had a sore throat and swollen glands which lasted two months. In 1934 he suffered from a sore on the lip, lasting three weeks, accompanied by a sore throat. No Wassermann test was taken, and he was well until December 1935. Two small papules on the left cheek and one on the nose appeared and since then the eruption has spread. At presentation there is an erythematous, infiltrated, nodular, serpiginous eruption with crusting and scaling on the arms, chest, back, trunk and legs, also on the back of the neck, the left cheek, nose and about the hair line. The papules appear to be copper colored. There is some nodular atrophy. Wassermann and Kahn tests on May 2, 1936, were positive, 4 plus. A biopsy of the lesion was made on May 4, 1936, and revealed hyperkeratotic secondary syphilis.

DISCUSSION

DR. GEORGE M. MACKEE: I agree with the diagnosis of a late secondary or early tertiary syphilis.

DR. LUDWIG OULMANN: The result of two injections of a bismuth preparation shows that those cases respond more readily to treatment than some of the cases of early syphilis.

DR. HOWARD FOX: I think this is a classic case of a serpiginous nodular (tertiary) syphilid. As it is a destructive process, it should be followed by atrophy.

PHILADELPHIA DERMATOLOGICAL SOCIETY

HERBERT J. SMITH, M.D., *Chairman*

May 15, 1936

VAUGHN C. GARNER, M.D., *Secretary*

GENERALIZED ICHTHYOSIS. Presented by DR. B. L. KAHN for DR. MAURICE BROWN.

W. W., a man aged 23, presents an eruption involving the whole body with the exception of the genitalia, palms and soles. The face shows a branny desquamation. The skin is dry, rough, somewhat thickened and covered with yellowish brown scales. There are some deep furrows and fissures on the legs. The condition has been present since birth. It is aggravated by exposure to cold, while in the summer it improves.

Serologic tests of the blood gave negative results. The sugar content of the blood was 87 mg., and the urea nitrogen content was 16 mg., per hundred cubic centimeters.

DISCUSSION

DR. DAVID M. SIDLICK: While the history agrees generally with the diagnosis of ichthyosis, the patient presents quite a number of clinical features which do not entirely fit in with that picture. For instance, the hands present acute inflammatory changes; the face is red and smooth, and there is considerable desquamation.

DR. VAUGHN C. GARNER: I thought the patient presented quite a bit of subepidermal erythema or flushing, which suggested to me the possibility of congenital ichthyosiform erythroderma.

DR. SIGMUND S. GREENBAUM: I suggest that a biopsy be made and the section compared with one showing ordinary ichthyosis. I think Dr. Garner's diagnosis would fit in well on clinical grounds alone. The diffuse hyperhidrosis and the diffuse erythema suggest an ichthyosiform hyperkeratosis rather than a simple ichthyosis, and the histologic examination should make it possible to differentiate between the two.

DR. EDWARD F. CORSON: I agree with Dr. Garner. Some years ago when Pautrier was in this country he presented under that title a case of a disorder similar to that exhibited by this patient.

ALOPECIA TOTALIS. Presented by DR. B. L. KAHN for DR. MAURICE BROWN.

R. G., a woman aged 27, presents complete denudation of the scalp. The eyebrows and eyelashes are absent except for a few scattered small hairs. The axillary and pubic hairs are sparse. The patient had practically all the childhood diseases and had pneumonia many years ago. In 1933 pleurisy with effusion developed on the left side; this was followed by all the characteristic signs of pulmonary tuberculosis. The hair began to fall out in patches after the patient had "infantile paralysis" at the age of 6 years and continued to fall out till three years ago, when all the scalp hair was lost.

The sputum contained tubercle bacilli.

All types of local therapy, including massage and ultraviolet irradiation, have been used without avail.

DISCUSSION

DR. WILLIAM O. ROOP, Atlantic City, N. J.: It is my impression that there have been cases in which the condition was of as long standing as fourteen years and in which the hair returned. I wonder whether the patient received roentgen therapy. That might have had some bearing on her alopecia.

DR. B. L. KAHN: She has received roentgen therapy. This woman became a patient of Dr. Schamberg twenty-one years ago.

DR. WILLIAM O. ROOP, Atlantic City, N. J.: Some years ago I saw a boy about 16 who had alopecia totalis which had resisted all treatment. He also had an undescended testicle, which was operated on. Within a month after the operation the hair began to grow, and the patient now has a complete return of hair. I do not know whether or not the operation had anything to do with the return of the hair, but I mention the fact as a point of interest.

DR. SIGMUND S. GREENBAUM: I think there may have been a connection between the correction of the undescended testicle and the return of hair, because there are many cases on record in which a reflex has occurred; for instance, removal of malposed teeth has been followed by growth of hair. As regards prognosis, the patients I have seen who have been bald for four years or more have rarely, if ever, had a return of hair. Sabouraud, I think, stated that after the fourth year there is practically no hope that the hair will grow again.

DR. VAUGHN C. GARNER: I feel as Dr. Greenbaum does with reference to the prognosis, but some years ago I observed a case in which a nurse aged about 20 had had alopecia totalis since the age of 10 years. I gave her no encouragement but suggested that she take a pituitary preparation and receive ultraviolet radiation. For six months she took a proprietary soluble extract of the anterior lobe

of the pituitary, but no evidence of return of hair was observed; however, she continued to receive ultraviolet radiation throughout the entire duration of her training. Subsequently she returned to my office, and to my amazement the largest proportion of her hair had grown again. I have seen this patient subsequently at intervals of a year, and she still retains three fourths of her hair. On the basis of this one case, therefore, I am not quite so dogmatic in reference to the poor prognosis.

DR. ABRAM STRAUSS: Does Dr. Garner attribute the return of hair to the pituitary medication?

DR. VAUGHN C. GARNER: No, because it was from six to eight months after the medication was stopped that hair began to grow.

DR. ABRAM STRAUSS: I treated a girl with the aforementioned pituitary preparation and ultraviolet radiation, and a perfect result was obtained. Six months later she again lost her hair. Since then I have been treating her with ultraviolet radiation alone, and the hair is growing again.

HYPERHIDROSIS. Presented by DR. J. E. COPELAND for DR. THOMAS BUTTERWORTH, Reading, Pa.

E. M., a boy aged 13, has dermatophytosis of the hands and feet and almost constantly shows excessive perspiration associated with redness over the bridge, tips and sides of the nose. The nose is cool to the touch. There is also some hyperhidrosis of the lower frontal region. The condition is not influenced by seasonal changes but the patient noticed that it is more pronounced when he is eating. He is uncertain as to its duration but states that it has apparently become worse in the last two years. Aside from the hyperhidrosis and erythema there are no demonstrable changes in the skin over the area affected. The patient also suffers from an associated vasomotor rhinitis and is sensitive to chicken feathers, horse dander, house dust, sheep wool, kapok, June grass and orchard grass. He is mentally subnormal. His speech is slurred. Neurologic examination revealed bilateral nystagmus, unequal knee jerks and spasticity and tremor of the fingers of the left hand. The pupils reacted sluggishly to light.

DISCUSSION

DR. THOMAS BUTTERWORTH, Reading, Pa.: When I first saw this boy he presented himself because of ringworm of the hands and feet, and I noticed that his nose was dripping wet with perspiration. He also had a mucopurulent discharge from the nose. My co-workers and I thought of some connection between the nasal condition and the sweating. Tonight he does not show the sweating, possibly because the rhinologist cleaned his nose out so well. However, I understand that a vasomotor rhinitis recurs promptly after treatment.

DR. SIGMUND S. GREENBAUM: I think this is a case of granulosis rubra nasi without the granulosis. Erythema and sweating are present even now; the nose is cold, probably owing to the rapid evaporation of sweat. Hyperhidrosis and redness localized to the nose before puberty really suggest an abortive form of granulosis rubra nasi.

DR. EDWARD F. CORSON: Usually granulosis rubra nasi affects malnourished children. I inquired of this boy's father, who said that the patient had always been healthy and rather well developed.

LICHEN NITIDUS. Presented by DR. SIGMUND S. GREENBAUM.

E. H., a Negress aged 23, sought medical advice for urticaria. During the course of examination the condition for which she is presented was noticed. Scattered over the trunk, the upper extremities and the back of the neck are a number of flat rounded discrete papules from the size of a pinpoint to that of a pinhead which are slightly paler than the normal skin. Some are arranged in linear formation along the marks of scratching on the abdomen. Those on the back of

the neck show some tendency to grouping. They are nonpruritic, and the patient is uncertain as to their duration. The tongue exhibits several pigmented areas and here and there evidence of superficial leukokeratosis. The physical examination gave essentially negative results. The patient suffers from recurrent urticaria induced by certain foods and exhibits well marked dermographism.

DISCUSSION

DR. SIGMUND S. GREENBAUM: The histologic picture is fairly characteristic. The interesting thing, of course, is to theorize about the etiology of this generalized papular eruption with a tuberculoid structure and its relationship to some of the more marked manifestations of cutaneous nodular tuberculosis. The main question in my mind is whether the lesions represent an id in the same way that the trichophytids are related to trichophytosis.

LUPUS ERYTHEMATOSUS. Presented by DR. C. O. RICH for DR. THOMAS BUTTERWORTH, Reading, Pa.

I. B., a Negro aged 42, presents hyperpigmentation over the butterfly area of the face. He has verrucous lesions and scars on the chest, above both eyes, in the left posterior auricular area and on the upper portion of the right arm. The hypertrophic lesions are pruritic and tender. He has dermatophytosis of the feet. He had a penile lesion in 1936 which was treated locally and orally. In 1927 there appeared below the left eye a dime-sized reddened area, which soon became verrucous. In 1928 similar lesions appeared around the right eye, in the hair line of the forehead and behind the left ear. In 1929 lesions appeared on the lips, chest and upper portion of the right arm. Roentgen examination of the chest showed healed pleuritis of the base of the left lung and enlarged tracheobronchial nodes.

Laboratory examinations for tuberculosis and serologic tests of the blood gave negative results.

DISCUSSION

DR. DAVID M. SIDLICK: I do not quite agree with the diagnosis of lupus erythematosus. I do agree with Dr. Butterworth as far as the eruption on the face is concerned—it looks like lupus erythematosus. But the lesions on the arms, those on the chest and particularly those on the forearm are elevated and do not show any signs of atrophy. I think the lesions on the chest and those on the arms are lupus vulgaris, and perhaps the condition on the face, too, might be included in the same picture.

DR. THOMAS BUTTERWORTH, Reading, Pa.: The patient has received a few injections of gold sodium chloride. I should not have called the lesions on the chest lupus erythematosus until a few months ago, when there were published several articles on lupus erythematosus in Negroes and some one from the South discussed the occurrence of hypertrophic scarring in cases of lupus erythematosus in Negroes.

DR. SIGMUND S. GREENBAUM: The patient was lost sight of for a while a few years ago and received some injections of an antisyphilitic preparation at another hospital, as a result of which tremendous improvement was observed in the lesions. Apparently a relapse occurred later. However, the lesions on the palate, on the ears and in the butterfly area certainly suggest that the whole picture is one of lupus erythematosus with hypertrophic scarring in the lesions on the chest.

SUBCUTANEOUS FIBROID SYPHILOMA. Presented by DR. CLEMENT COUNTER for DR. SIGMUND S. GREENBAUM.

E. B., a man aged 41, says that six weeks ago there developed in the skin nodules which grew gradually worse until about ten days ago, when they seemed to improve. The patient's wife is receiving antisyphilitic treatment. When she was found to have syphilis the Wassermann reaction of the patient's blood was

negative. Later a sore developed on his lip and shortly thereafter a generalized rash and a positive Wassermann reaction of the blood appeared. He was given bismuth subsalicylate weekly; this cleared up the sore on the lip and the rash.

The Wassermann reaction of the blood was 444. A biopsy showed a chronic infectious granuloma compatible with, but not diagnostic of, syphilis. The patient has received no treatment other than bismuth subsalicylate.

DISCUSSION

DR. SIGMUND S. GREENBAUM: This is an interesting case. When the patient presented himself he had a primary lesion on the lip and a generalized macular eruption of secondary syphilis. He was given bismuth therapy, and during the course of that treatment subcutaneous nodules developed quite profusely over the body, and in one or two areas there appeared cutaneous nodules such as are now on the right arm. These nodules are suggestive of gummatous nonulcerative tertiary lesions. My co-workers and I assumed that we were dealing with multiple subcutaneous fibrosyphilomas developing early, and, curiously, many of those lesions disappeared and a certain number of them are well on the way to involution. A specimen for biopsy has been taken, but no report has been made as yet. The only case I know of multiple subcutaneous fibrosyphilomas was described by Weber some years ago in the *British Journal of Dermatology*. It is unusually early in the disease for lesions of that type to develop.

DR. ABRAM STRAUSS: Has the patient received any arsenic?

DR. SIGMUND S. GREENBAUM: Not yet, but the lesions are involuting as a result of the bismuth therapy, and it has been continued.

DR. VAUGHN C. GARNER: I was under the impression that the subcutaneous fibroid syphilomas described by Weber were identical with the juxta-articular nodes described by Jeanselme.

DR. SIGMUND S. GREENBAUM: The difference is in the multiplicity and in the location of the lesions.

DR. VAUGHN C. GARNER: I wondered whether the disorder could be interpreted as a precocious tertiary stage, that is, a Herxheimer reaction induced by bismuth and subsiding as a result of further treatment.

DR. SIGMUND S. GREENBAUM: As the eruption appeared after fifteen or sixteen injections, it seems to be a manifestation of tertiary syphilis, but I hardly think that it is a Herxheimer reaction, because the secondary lesions disappeared, and a Herxheimer reaction is a stimulation of active lesions rather than a recurrence during treatment.

DR. THOMAS BUTTERWORTH, Reading, Pa.: I was interested in this case from the point of view of the distribution of the lesions. I think Dr. Greenbaum has made a good case for a syphilitic manifestation, but in examining the patient tonight I found that these subcutaneous nodules appeared in parts of the body that were injured in an explosion a few years ago—over the scapula, between the shoulder blades and fairly well down on the back there were no lesions at all, but on the flank there were scars similar to those in the anterior surfaces of his body, and in the neighborhood of those scars the nodules were present. On the back I could not find any, but the whole anterior surface of the body seemed to be studded with these nodules. I wondered whether the trauma sustained years ago had anything to do with the localization of these nodules or whether the nodules in the healthy portion of the skin had cleared up and disappeared.

DR. SIGMUND S. GREENBAUM: There is a possibility that the trauma had something to do with the appearance of the nodules, but the history and the fact that they are disappearing would certainly exclude any nodulation due to a foreign body. The effect of trauma in this case is shown clearly by the tertiary lesion in the right antecubital region where blood was taken, also on the forehead where the patient sustained an injury. The latter is a remarkable instance of the effect of trauma in a patient with acute syphilis. I have seen this precocious tertiary stage in cases of cerebral lesions and of lesions of the spinal cord. Cases have been reported of dementia paralytica developing in a year or two.

DEPILATING FOLLICULITIS OF THE LIMBS (ARNOZAN) AND PSEUDOPELADE OF THE LIMBS. Presented by DR. C. O. RICH for DR. SIGMUND S. GREENBAUM.

D. M., a man aged 43, entered the hospital in May 1935 because of a gastric ulcer. During the five weeks of his stay pustular folliculitis developed over the thighs and legs. At present there are over the thighs and legs areas showing loss of hair with follicular atrophy but no folliculitis.

The Wassermann reaction of the blood was negative. A biopsy showed subacute diffuse dermatitis.

DISCUSSION

DR. SIGMUND S. GREENBAUM: This is probably the first case of this disorder that has ever been presented before this society. It is the first I have ever seen. Knowles is the only author who in his textbook on dermatology refers to a depilating folliculitis of the limbs described originally by Arnozan in France. The resemblance to the end-results of keratosis pilaris is close. On close inspection of the thighs one notes the evidence of cicatricial alopecia without evidence of inflammation, and in other areas one sees inflammatory zones and alopecia—in other words, there is a combination of pseudopelade and folliculitis decalvans. It is likely that pseudopelade and folliculitis decalvans are the same process, the only difference being in the virulence of the staphylococcus producing it. One can see the original pinhead atrophic areas not only in the inflamed but also in the non-inflamed sites.

RESULTS OF TREATMENT OF LUPUS SERPIGINOSUS AND ELEPHANTIASIS BY ELECTROCOAGULATION AND PLASTIC SURGERY. Presented by DR. THOMAS BUTTERWORTH, Reading, Pa.

G. N., a woman aged 25, says that when she was aged 16 an ulcer the size of a 25 cent piece developed on her left leg. This was followed by a succession of similar lesions. In the summer of 1934 the left lower extremity was enlarged in its entirety, but the excess growth was particularly abundant about the ankle. On all aspects of the thigh and about the knee were numerous serpiginous, gyrate, and annular verrucoid and crusted lesions of lupus. In places there were small ragged dirty and foul-smelling ulcerations with abundant crusting, and a deep purulent ulcer was present on the outer aspect of the left leg. The lesions had a tendency toward peripheral extension with the formation of central flat atrophic scars. Recurrence had taken place within the scars in several places. The swelling of the limb was firm and did not pit on pressure. A Mantoux test made at that time produced a wheal 1 cm. in diameter as an immediate reaction. After forty-eight hours an area of papules measuring 1 cm. and an area of erythema measuring 2.5 cm. had appeared. Wassermann tests of the blood and smears for blastomycosis gave negative results, and roentgenograms of the chest and of the bones of the leg showed no abnormalities. A biopsy showed the picture of tuberculosis cutis. The patient had faithfully adhered to a salt-free diet and had taken phosphorized cod liver oil for many months. Many injections of gold and sodium thiosulfate and roentgen and ultraviolet irradiation had failed to halt the process. On three occasions, the patient being anesthetized with gas, the lesions on the leg, on the inner side of the thigh and on the outer side of the thigh were successively (Oct. 22, 1934, Nov. 23, 1934, and Jan. 15, 1935, respectively) destroyed by currettage and electrocoagulation, after which finely pulverized potassium permanganate was applied. Healing was slow but uneventful. Within the past ten months four Kondoleon operations have been performed on the left leg and thigh. At the first of these, in July 1935, 966 Gm. of skin, superficial fascia and subcutaneous fat was removed by means of an incision extending from the superior part of the iliac portion of the spine to the external malleolus. Subsequent operations were performed about the ankle. In all, about 1,500 Gm. of tissue were removed. Many histologic studies were made on the excised tissue, but no evidence of a granulomatous process was observed. The cosmetic appearance of the limb has been greatly improved. The ankle is still larger than its fellow, but the tough fibrous nature of the tissue in that region rendered further plastic work

inadvisable. Subcutaneous injections of Locke's solution according to the method of Biegeleisen were considered in an effort to reduce the fibrolymphedema about the ankle.

DISCUSSION

DR. THOMAS BUTTERWORTH, Reading, Pa.: The patient has received the usual palliative treatment for lupus vulgaris, strictly following the regimen, the saltless diet and receiving injections of a gold preparation, but as the lesions were progressing, I thought, in view of the success I had with electrocoagulation and rubbing in of pulverized potassium permanganate on smaller lesions, that it might be well to try those measures on this patient, progressing gradually. In the winter of 1934-1935 I electrocoagulated the whole of the areas which are now involved. When I presented this patient at a previous meeting of this society the leg was still enormously hypertrophied. Beginning last July, a surgeon started to perform the Kondoleon operations. The big problem remaining is the condition of the ankle. By making careful measurements at corresponding points on the thighs and around the knees it is seen that there is not a great amount of difference between the two legs, but at the ankles there is still room for much improvement. After the last operation a mild infection developed in two wounds which have not healed entirely, but I expect them to clear up soon. The next thing I plan to do is to inject the Locke solution around the ankles, as was advocated in a recent paper. I have never had any experience with this technic, and if any of the members has tried it on lymphedema from any cause, I should like to hear his opinion.

DR. CLAUS JORDAN, Stroudsburg, Pa.: My co-workers and I have had several patients with elephantiasis on our service and have performed a number of Kondoleon operations; some have been successful and some have not. Involvement of the ankle was always the hardest to control. I had one patient with really acute elephantiasis whom I treated with injections of Locke's serum with great success. That man was almost cured within six weeks without any Kondoleon operation. After twenty years Kondoleon himself has had only about 50 per cent success with all his operations. In many cases the disorder recurs. The success of the operation, I think, depends definitely on taking away the skin, but later on, if any infection remains, the condition recurs. It is the infection of the subcutaneous tissues plus the lymphedema that causes the disorder.

DR. SIGMUND S. GREENBAUM: I should like to ask Dr. Butterworth whether the subcutaneous tissue was examined histologically. I was under the impression that this patient had only tuberculosis of the skin without tuberculous lymphangitis.

DR. THOMAS BUTTERWORTH: The pathologist has made about twenty or more sections from different pieces of tissue, and each time the report has been "No granulomatous process demonstrated." I have watched for evidence of recurrence of the tuberculosis.

CHICAGO DERMATOLOGICAL SOCIETY

MAX S. WIEN, M.D., *President*

May 20, 1936

RUBEN NOMLAND, M.D., *Secretary*

TUBERCULOUS COMPLEX (PRIMARY?). Presented by DR. RUBEN NOMLAND and DR. F. J. KENDRICK, Gary, Ind.

This obese Italian girl, aged 12 years, presents a disorder which began in September 1935 as a crusted furuncle-like lesion on the outer aspect of the right forearm. Shortly thereafter the axillary lymph glands became enlarged. The mother states that when the patient was a small child she had a boil in her right axilla, which was evacuated and healed in a few weeks.

When she was first seen by us, about eight weeks ago, she had a dime-sized scar with a red border on the extensor surface of the right forearm. On pressure

with the diascope the lesion showed apple jelly brown nodules. In the axilla the glands were the size of a pigeon's egg, firm and not tender or red. In the course of four weeks the glands enlarged and became red, and recently they broke through the overlying skin. An intracutaneous test with 0.05 cc. of a 1:1,000 dilution of old tuberculin gave a strongly positive reaction.

DISCUSSION

DR. JAMES H. MITCHELL: There is no way of knowing, I suppose, what the reaction to tuberculin was before Dr. Nomland examined the patient. If the lesion is a tuberculous chancre it gives information as to the patient's hygienic surroundings.

DR. RUBEN NOMLAND: The diagnosis remained in abeyance for some time, and Dr. Ebert was the first to suggest that the lesion was a primary tuberculous complex; Dr. Ormsby agreed with that diagnosis. The patient is not cooperative, and I doubt that it will be possible to make a much more complete examination.

POIKILODERMA ATROPHICANS VASCULARE. Presented by DR. MINNIE O. PERLSTEIN (by invitation).

This Jewess, aged 48, was presented at the clinical session of the American Dermatological Association on June 10, 1933 (ARCH. DERMAT. & SYPH. **29**:158 [Jan.] 1934).

She is presented now to show the progress of the dermatitis. The eruption is generalized, and there is almost no normal skin apparent except over the forehead, nose and chin. The character of the eruption remains essentially the same as at the previous presentation, and the patient's general health has remained unchanged.

POIKILODERMA ATROPHICANS VASCULARE. Presented by DR. MAX S. WIEN, DR. MINNIE O. PERLSTEIN (by invitation) and DR. A. SLEPYAN.

This Greek woman, aged 35, presents an asymptomatic progressive eruption of about four years' duration consisting of discrete, roughly symmetrical, round plaques varying in size from that of a palm to that of a plate. It involves the breasts and thighs and is diffusely scattered over the shoulders and back. The affected areas show reticular atrophy and telangiectasia, the condition resembling roentgen ray dermatitis. The color varies from red to violet and brown.

The patient's general condition is unusually good. She has been in the United States for eighteen years. Her husband and one son aged 13 are living and well. She states that the cutaneous disorder began six months after she had a spontaneous miscarriage four years ago. She states that she suffers from disturbances referable to the gallbladder. Therapy with an ovarian preparation caused her to gain weight; she then stopped treatment. Her weight remains fairly standard.

Repeated Wassermann tests of the blood have been negative. The basal metaboic rate was —18 per cent.

A biopsy specimen removed from a lesion on the breast revealed a loosely adherent hyperkeratotic scale. The epithelium was for the most part atrophic; the rete pegs and the rete cells were flattened. In some areas intra-epithelial vascular degeneration was evident. The cuto-epithelial junction was indistinct in some areas. In the papillary zone about the dilated vessels were numerous pyknotic fibrocytes, lymphocytes, chromatophores filled with golden yellow pigment and an occasional mast cell. The collagen fibers in this area were rarefied and pigmented. Degenerative changes were noted throughout the cutis. Disrupted, clumped pigments were all that represented the elastic fibers about the infiltrate.

DISCUSSION

DR. F. E. SENEAR: I saw the second patient about a year ago. Dr. Oliver saw her with me, but neither of us has definite recollection of the case or of what we thought about it then. I recall rather dimly that at that time the patient did not show the picture to the degree that is now present on the breasts, and I believe

we considered parapsoriasis as a possible diagnosis. I think this case exemplifies again something which has often been discussed before, namely, that many of these disorders have to be differentiated from poikiloderma-like conditions. The first patient still shows some of the infiltrated patches on the arm. In the second case I agree with the diagnosis as presented.

DR. E. A. OLIVER: I think both of these patients exhibit a disorder which approaches the original description given by Jacobi of poikiloderma atrophicans vasculare; the picture resembles that condition as nearly as any exhibited by patients presented before this society. I was much interested in seeing the first patient again, because when this patient was first presented there was some possibility that infiltrated lesions of mycosis fungoides were developing. It is interesting to see two such good examples of the disorder, for, as I pointed out, during the last year there have been presented before local societies numerous patients whose disorders were classified as poikiloderma atrophicans vasculare whereas they should have been termed poikiloderma-like conditions. Poikiloderma is a rare disease, but poikiloderma-like conditions are not rare. These can be grouped in three divisions as follows: (1) True poikiloderma atrophicans vasculare, as described by Jacobi. In association with this type such conditions as myositis may enlarge the original picture. (2) Disorders that are nevoid in type. (3) Disorders causing poikiloderma-like symptoms that are part of the picture of some chronic constitutional disease such as mycosis fungoides and leukemia.

DR. M. H. EBERT: I had an opportunity to study the sections Dr. Slepyan prepared in the second case, and the changes were certainly consistent with those described in cases of poikiloderma atrophicans vasculare.

PEMPHIGUS FOLIACEUS ET VEGETANS ASSOCIATED WITH ARSENICAL DERMATITIS. Presented by DR. M. E. OBERMAYER.

This man, aged 27, of Italian extraction, states that seven years ago there developed on the abdomen an eruption which spread rapidly to the remainder of the body. From two to three months after the onset bullous lesions appeared on the legs, arms and back. These lesions varied considerably in size. Since that time the eruption has never entirely disappeared. The patient was hospitalized at the Cook County Hospital six and again three years ago for several months at a time.

There is a generalized eruption consisting of flaccid epidermis forming polycyclic outlines with central crusting, interspersed with intact bullae of various sizes. The skin is markedly thickened in some areas. General lymphadenopathy is present. There are no lesions of the mucous membranes. Vegetative lesions having a fetid purulent odor are present behind the ears and are scattered diffusely over the scalp. On the palms and soles are groups of arsenical keratoses.

Examination of the blood showed that the number of leukocytes varied between 10,400 and 18,900. The differential count showed considerable eosinophilia at times and a moderate shift to the left. Urinalysis gave negative results.

Treatment has consisted of extraction of devitalized teeth; administration of typhoid vaccine, which had no effect; McDonough therapy, which caused marked aggravation; roentgen therapy; generalized ultraviolet irradiation, and high caloric diet. At present the patient is receiving intravenous injections of ammonium succinimido-aurate.

A specimen of blood was sent to Dr. Welsh, of the Mayo Clinic, who made a diagnosis of dermatitis herpetiformis.

Specimens for biopsy were taken from the right leg and from a lesion on the back. Both slides are presented; they show the changes usually seen in this form of the disease.

DISCUSSION

DR. E. A. OLIVER: I think it is interesting that this man is still alive. As I recall, he had quite an extensive pemphigus when he was presented before this society several years ago. I wonder whether any of the members is trying the treatment with snake venom. There is a patient at the Veteran's Administration

Facilities in whom all therapy previously used failed to produce improvement; during the past month my colleagues and I have treated him with moccasin venom, and I think he has shown more improvement as a result of that than of any other therapy.

DR. THEODORE CORNBLEET: When this patient was in the hospital before he certainly did not show as much pigment as he exhibits at present, and I remember quite definitely that he showed a Nikolsky sign. In regard to Dr. Oliver's remark concerning the use of venom, I tried it in one of my patients last year without any results. The patient died.

DR. JAMES H. MITCHELL: It seems to me a patient who for seven years has had as severe an eruption as this man exhibits probably has something other than pemphigus. I am inclined to believe that he has dermatitis herpetiformis.

DR. E. A. OLIVER: I believe that this man shows a fairly typical picture of pemphigus. I have observed cases previously that have lasted for a number of years, and I do not believe that the duration of the condition necessarily rules out pemphigus.

DR. M. J. REUTER: I agree with the diagnosis of pemphigus.

DR. MAX S. WIEN: I recall that this patient was on my service at the Cook County Hospital in 1930 and in 1932. A Pels-Macht test showed a phytotoxic index of 54. On referring to his record I also find that the eosinophil count was as high as 25 per cent. While he was on the service he presented a varying picture with exfoliation, a positive Nikolsky sign and the odor of pemphigus. The extreme pigmentation was commented on when he was previously presented before this society. He was treated with acetarsone for a time because of the difficulty in making injections into his veins. Extreme itching was present. The diagnosis rested between dermatitis herpetiformis and pemphigus foliaceus, and the clinical picture at that time pointed to the latter diagnosis. Eighteen months ago I observed a generalized bullous eruption in a man who had a strongly positive reaction to the Welsh test for pemphigus. The man completely recovered from his attack and has had no lesions since. Dr. Welsh reported that the reaction was one of the strongest he had observed.

DR. RUBEN NOMLAND: I think I have sent Dr. Welsh twelve or fifteen serums, and his diagnosis agrees with the clinical diagnosis in from 85 to 90 per cent of the cases.

DR. MAX S. WIEN: The results of Dr. Welsh's tests on the serums submitted have agreed with the clinical diagnosis in all the cases in which I asked him to make the test, except, perhaps, in the one I mentioned. I believe that the test is more specific than the Pels-Macht test. In the case mentioned the clinical picture at the time the serum was obtained was that of acute butcher's pemphigus. This picture appeared after a severe erythema multiforme occurred which followed the extraction of a tooth. It is still an open question whether the man had pemphigus, with recovery or remission, or erythema multiforme bullosum. He has remained well since recovery occurred eighteen months ago.

DR. M. E. OBERMAYER: The picture of pemphigus foliaceus et vegetans which the patient presents is difficult to reconcile with a possible diagnosis of dermatitis herpetiformis. But, as Dr. Mitchell has pointed out, the disorder has been going on for so many years that one may doubt whether it is true pemphigus. This thought is emphasized by the result of the Welsh test, which in my experience has been very reliable, especially in the last four months. I appreciate Dr. Oliver's suggestion as to treatment with moccasin venom.

SARCOID IN A NEGRESS. Presented by DR. RUBEN NOMLAND.

This Negress was presented before the society several years ago (ARCH. DERMAT. & SYPH. (**26**:1119 [Dec.] 1932). At that time she exhibited about twenty nodular lesions located chiefly on the extensor aspect of the arms and forearms. Three more superficial lesions were present on the face. The disorder was then of three years' duration. There was hoarseness associated with infiltration of the larynx. A biopsy showed a typical sarcoid structure of the Darier type.

During the past four years the condition has progressed. Almost all the subcutaneous nodules on the arms have developed into infiltrated plaques, which have attained a diameter as great as 10 cm. Several more superficial annular lesions have developed on the face. Numerous new lesions consisting of superficial red lichenoid papules and larger round papules up to 6 mm. in diameter have appeared on the posterior aspect of the neck.

A roentgenogram of the chest revealed some fibrosis and increase in markings. The bones of the hands were normal. The patient's general condition and health have remained good. She was relatively insensitive to tuberculin, 0.05 cc. of a 1:100 dilution of old tuberculin causing only a slight reaction.

No new biopsy has been made.

DISCUSSION

DR. A. W. STILLIANS: The disorder looks to me like nonulcerative lupus vulgaris. I did not see the section.

DR. MARCUS R. CARO: I think the histologic picture is that of sarcoid.

DR. F. E. SENEAR: Are the photographs which Dr. Nomland showed pictures of the same patient taken several years ago and had the lesions which appeared to have done so broken down?

DR. RUBEN NOMLAND: Several of them had broken down.

DR. F. E. SENEAR: I asked this question because both Dr. Caro and I were impressed with the fact that this particular lesion was a duplicate of one we have recorded in photographs and lantern slides in the case of a woman with tuberculosis colliquativa. In that case several of the lesions had broken down and produced a lesion which was clinically a counterpart of that on the forearm of this patient. In our case there was no sarcoid.

DR. RUBEN NOMLAND: If I recall correctly, approximately five of the lesions eroded the overlying skin, not in the way that tuberculosis colliquativa does, but rather, it seemed, because of a disturbance in the circulation. A point of great interest in this case is that the patient has all sorts of lesions—papules, plaques and superficial annular lesions—in addition to the deep lesions. The most interesting feature is the fact that in the larynx and nose she has lesions in which the same typical sarcoid structure is present. I think there is not much evidence in favor of a diagnosis of multiple gummatous tuberculous lesions.

MELANOMA OF THE FOOT. Presented by DR. JAMES H. MITCHELL.

This woman, aged 56, was first seen on May 11, 1936, exhibiting a pigmented lobulated freely movable lesion crusted with blood on the outer margin of the left foot. A pigmented lesion had been present at the same site for many years. Several months ago the patient rubbed the lesion "real hard," breaking the skin and causing the lesion to bleed.

On May 11, 1936, 700 roentgens of radiation filtered through 1 mm. of aluminum was given to the lesion. No other treatment of any kind has been administered.

DISCUSSION

DR. L. F. WEBER: I think the disease is malignant, but I am inclined to classify it as carcinoma.

DR. M. H. EBERT: I should like to know if there was a lesion on this site originally. If there was, I should be inclined to make a diagnosis of melanoma.

DR. M. J. REUTER: If the history is correct, I agree with the diagnosis of malignant melanoma. The question that always arises is what to do in a case of melanoma, as opinions differ widely. I should want to see a section, and I should immediately apply surgical diathermy to destroy the lesion and perhaps 1 inch (2.5 cm.) or more of the normal skin surrounding it. Then I should hope I had done something for the patient.

DR. M. E. OBERMAYER: I feel that Dr. Reuter's method would not be safe enough. I should excise the lesion and remove the regional lymph nodes.

DR. E. A. OLIVER: We have discussed this subject time and time again, and all the members know that physicians invariably excise such lesions without traumatizing them. One of the most successful outcomes I have seen in a case of melanoma, the patient being alive and well, was the result of intensive treatment with radium to the lesions and to the adjacent glands. I believe that if this woman were my patient I should use radium therapy.

DR. A. W. STILLIANS: I agree with Dr. Oliver that radiotherapy is the safest method. I have a patient, a young boy with a thumb-sized lesion on the right cheek which was treated about five years ago with intensive roentgen and radium therapy. I used as much radiation as I dared. The patient had a severe reaction, and some tissue atrophied, but he is well. The scar measures about 5 cm., but no glands are palpable so far.

DR. RUBEN NOMLAND: In over 40 per cent of the cases of melanoma which my co-workers and I observed at the Rush Medical College the lesions have been on the foot, and the heel appeared to be the favorite site. In most cases the disease had progressed beyond the favorable time, and we have taken a specimen for biopsy, believing that that could not do harm. In several cases there has been no history of a preceding mole of any type. I have witnessed a three year cure in a case of malignant melanoma of the arm. The lesion, a dark mole about the size of a pea, had enlarged for three months. It was excised widely and then treated with intensive roentgen therapy, and up to the present there has been no recurrence.

DR. EUGENE P. LIEBERTHAL: I remember two cases of this condition; in one there was a lesion on the dorsum of the foot. The patient was presented before the society after he had received treatment with massive doses of radiation at the Northwestern University Medical School. I saw that boy two weeks ago, and the result is perfect. The other patient, a woman, had a lesion on the dorsum of the foot. She received high voltage roentgen therapy followed by superficial irradiation of the inguinal glands. She is still alive after five years, and the lesion is apparently healed.

DR. MAX S. WIEN: These lesions may take variable courses. About three years ago I saw a woman of 70 with a melanoma on the ball of the foot which had been trimmed by a chiropodist. She had a metastatic gland of hazelnut size in the femoral triangle. I advised that the lesion be left alone, as metastasis had already occurred. Several months later an abdominal condition that required operation developed, and abdominal examination revealed metastases in the abdominal glands. Since then the patient has had pneumonia and has recovered, and she has made several long journeys and is not greatly inconvenienced by the lesion or by the metastases.

DR. JAMES H. MITCHELL: This lesion is so young that I hesitate to take a specimen for a biopsy. I am satisfied that it is a melanoma, although there is not much pigment. I am sure that roentgen therapy is the most satisfactory method of treatment if it is carried out thoroughly. The most extensive melanoma I recall occurred on the forearm of a patient whom I saw in Dr. Ormsby's office many years ago. Last year I asked him about that patient, and he said she was still alive. She received only radiotherapy, and although the pigment remained, the lesion healed.

'The discussion on excision and metastasis with no recurrences in situ recalls a case also observed in Dr. Ormsby's office many years ago. The patient had a lesion on the scapula which was excised, and when my co-workers and I saw him he had general metastases. Some of the members who attended the meeting in San Francisco may remember having seen a woman with metastases which according to the attending physicians and the interns developed in the course of one night. I shall be conservative and for the present treat this lesion with filtered roentgen radiation.

Book Reviews

Lexicon der kosmetischen Praxis. Prepared by Local and Foreign Experts in Science and Practice Under the Editorial Direction of R. Volk and F. Winter (Vienna). Price, paper, 75 marks; bound, 80 marks. Pp. 706 (two columns). Berlin: Julius Springer, 1936.

This is practically an encyclopedia of the theory and practice of cosmesis, both surgical and nonsurgical. Apparently nothing is omitted, but the amount of space allotted to some of the subjects does not always agree with their importance. The contributors to this volume are not named, but they were called from many fields. Historical references are well presented and are given somewhat along the lines which Winter followed in his "Handbuch der gesamten Parfümerie und Kosmetik" (edition 2, 1932). The content, however, is thoroughly modern, including even the subject of hormones in cosmetics.

Many of the names appearing in the book are those of proprietary preparations. However, numerous cross-references are given so that the reader can obtain information on many unknown terms.

Both remedial and hygienic divisions are considered; in the latter, the care of normal skin is included.

The outline of procedures in cosmetic surgery is expertly presented, and illustrations are given.

The book is a definite contribution to a timely subject. As a source of reference it is without parallel, as it gives information about modern cosmetics, the ingredients used in their manufacture and their application. Unfortunately, it is in German, and the cost is practically prohibitive for wide circulation in this country.

Skin Diseases in Children. By George M. MacKee and Anthony C. Cipollaro. Pp. 345, with 153 illustrations. New York: Paul B. Hoeber, Inc., 1936.

Written to answer the needs of the physician in general practice, this book by MacKee and his younger associate, Cipollaro, is, as would be expected, essentially sound and altogether practical. It is a clinical work which is not overloaded with detail and places emphasis on the diagnosis and treatment of the diseases that are most frequently encountered. Descriptions of pathologic, anatomic or physiologic changes associated with the exanthemas are not included. Briefly, the book is a useful, informative, plainly written introduction to clinical dermatology as regards children, brought down to date.